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Review

Surface Modification of Biomedical Titanium Alloy: Micromorphology, Microstructure Evolution and Biomedical Applications

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Received: 12 March 2019; Accepted: 9 April 2019; Published: 15 April 2019

Abstract: With the increasing demand for bone implant therapy, titanium alloy has been widely used in the biomedical field. However, various potential applications of titanium alloy implants are easily hampered by their biological inertia. In fact, the interaction of the implant with tissue is critical to the success of the implant. Thus, the implant surface is modified before implantation frequently, which can not only improve the mechanical properties of the implant, but also polish up bioactivity and osseoconductivity on a cellular level. This paper aims at reviewing titanium surface modification techniques for biomedical applications. Additionally, several other significant aspects are described in detail in this article, for example, micromorphology, microstructure evolution that determines mechanical properties, as well as a number of issues concerning about practical application of biomedical implants.

Keywords: titanium alloy; surface modification; biomedical application

1. Introduction

In the past few decades, resulting from the aging of the population and the change of people's lifestyle, tens of thousands of people have been plagued by orthopedic, oral and maxillofacial diseases [1]. Thus, solving these problems enables patients to return to a high-quality life, and the demand for medical implants increases dramatically with the growing maturity of implant technology [2]. As scientists have predicted, more people will suffer from orthopedic diseases in the future and the annual economic costs will be particularly huge [3].

Today, as biomaterials are developing rapidly, biomedical materials can be mainly divided into metals, ceramics, bioactive glass, plastics and their combinations [4]. Among all biomedical materials, metal materials are the earliest applications and the most widely used in clinical practice [5]. Titanium alloy especially, compared with other metal alloys, has great advantages in mechanical properties, such as elasticity modulus, tensile strength, toughness, and fatigue resistance [6,7]. At the same time, titanium alloy has excellent corrosion resistance to physiological fluids and excellent biocompatibility, due to its oxidation film passivation stability [8,9]. In addition, biological responses of titanium alloy implants, such as bioactivity and osseointegration, are positive for clinical application [10]. Thus, it is not only widely used in dental implants, artificial joints and bone wounds, but also has become an important material for human body hard tissue substitutes. Moreover, with the continuous improvement and perfection of medical titanium alloys, the exploration of novel medical titanium alloys and the diversification of production technology will further expand their applications [11,12].

Although titanium-based alloys have excellent mechanical properties, the exposed surface of titanium-based implants is easily affected by the environment and may cause complications. Therefore, it is necessary to improve the reliability of Ti-based implants to minimize certain biomechanical and biological function failure [13,14]. In order to overcome its harm to human body, titanium alloy must be surface modified to meet medical application requirements. This review focuses on various surface modification methods such as plasma spray, ion implantation, micro-arc oxidation, laser surface modification, sol-gel, friction stir processing (FSP) and the practical biomedical applications of each technology.

2. Surface Modification Methods

2.1. Micro-Arc Oxidation

Micro-arc oxidation (MAO), forming a high-quality reinforced ceramic film on implant surface, is a relatively effective technique of the surface treatment in biomedical field based on anodic-oxidation [15,16]. The schematic diagram is shown in Figure 1 [17]. MAO has been widely studied in numerous fields including biomedical applications because the advantages of low-cost, high efficiency, high bonding strength between the MAO coating and substrate, no restriction on the surface shape of the workpiece and so on [18–20]. The microstructure and mechanical properties of micro-arc oxide film, which are mainly controlled by electrolyte type, matrix composition and process parameters, determine the interaction between implants and surrounding host tissues and is essential for cell adhesion, proliferation and differentiation [21–23].

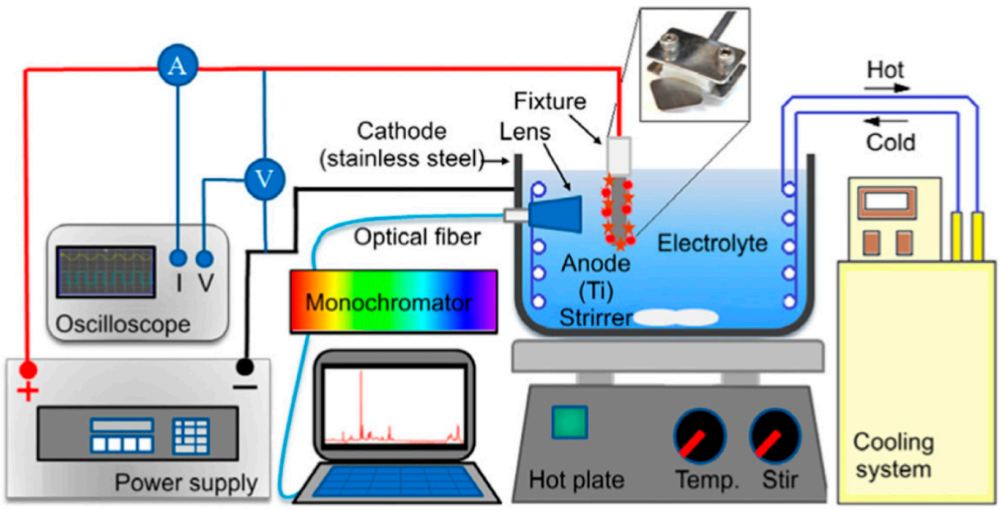

Figure 1. Schematic diagram of the micro-arc oxidation (MAO) process [17]. Reprinted with permission from reference [17] 2017 Elsevier.

Researchers have explored bioactive coating with suitable structure of medical implants that can improve the biocompatibility and shorten osseointegration time [24]. Xu et al. [25] prepared porous coatings with different roughness by controlling oxidation duration on Ti implants by MAO. The porous coating surface significantly promotes adhesion and proliferation of osteoblasts. Similarly, in order to create functional surfaces with antibacterial and osteogenic properties, Coquillat et al. [26] explored the effect of processing time on coating composition and morphology in two different electrolytes. Furthermore, Li et al. [27] studied the two-step micro-arc oxidation method to prepare super-hydrophilic biomedical coatings with macro/micro/nano three-layer structures. In addition, Wang et al. [28] and Sedelnikova et al. [29] prepared coatings on Ti-based alloy with different surface morphology, thickness and adhesion strength with MAO through controlling voltage. The SEM micrograph is shown in Figure 2. After MAO treatment, the implant has a promoting effect on cell adhesion, diffusion, proliferation and differentiation. In addition to oxidation duration, the composition of electrolyte and biological elements play a crucial role in biocompatibility.

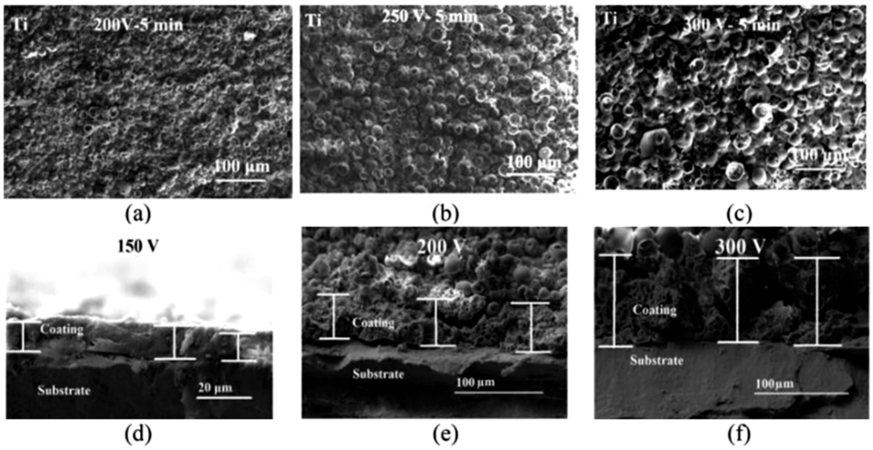

Figure 2. SEM micrographs of the wollastonite-calcium phosphate (W-CaP) coatings on Ti (**a**–**c**) and SEM micrographs of the cross-sectional W-CaP coatings on Ti (**d**–**f**) produced under different voltages [29].

Researchers have investigated the effect of electrolyte composition on the microstructure and properties of titanium matrix micro-arc oxidation coating. It is obvious that the composition of electrolyte affects the physical and chemical properties of the coating and the growth rate of the coating [30,31]. Recent research has shown that biological elements, such as Cu, Ca, Zr, P and Si are beneficial for improving the bioactivity of materials, further enhancing implant osseointegration [32–34]. Huang et al. [35] investigated bone regeneration and bactericidal capacity of MAO coatings on Ti in a Cu-containing electrolyte. Macrophage-mediated osteogenesis, macrophage polarization and macrophage bactericidal assay experiments showed that coating with higher content of Cu is more favourable for macrophage proliferation. Interaction between macrophages and bacteria on various surfaces are shown in Figure 3. The capture behavior of bacteria by macrophages is significant on the surface with high Cu content, which indicates that the bactericidal capacity of macrophages is promoted on the Cu-MAO surface.

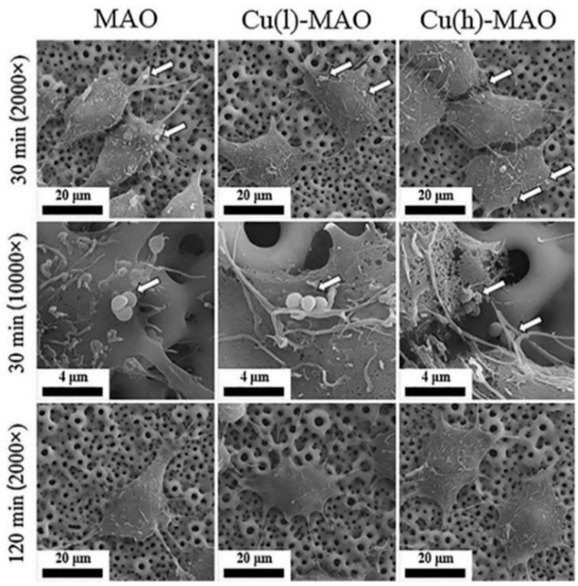

Figure 3. The bactericidal capacity of macrophages in response to material surfaces. The SEM images showing the macrophage/bacteria interactions on different Cu-containing surfaces. Respectively, specimens treated with 0.2 and 2 mM $CuSO_4 \cdot 5H_2O$ were recorded as Cu(l)-MAO) and 2(Cu(h)-MAO). The white arrows indicate that bacteria are captured by macrophages [35]. Reprinted with permission from reference [35] 2018 Elsevier.

The microstructure, morphology and mechanical properties of the micro-arc oxidation coating are affected by the alloying elements. Recently, Wang et al. [36] and Correa et al. [32] have studied the effect of Ti-based alloy composition on the growth mechanism of MAO films. Additionally, in order to obtain bioactive surfaces, Hu et al. [37] prepared multilayer $TiO_2/CaSiO_3$ coating on titanium substrate by MAO and electron beam evaporation. Surface morphologies are shown in Figure 4. The needle and flake-like nanocrystals $CaSiO_3$, which are considered a potential material for bone tissue regeneration, were deposited on TiO_2 coating by electron beam evaporation. To achieve antibacterial capacity and cytocompatibility, an implant with gradient structure of $Ti/TiO_2/ZnO$ was developed by MAO followed by hydrothermal treatment, as reported by Zhang et al. [38].

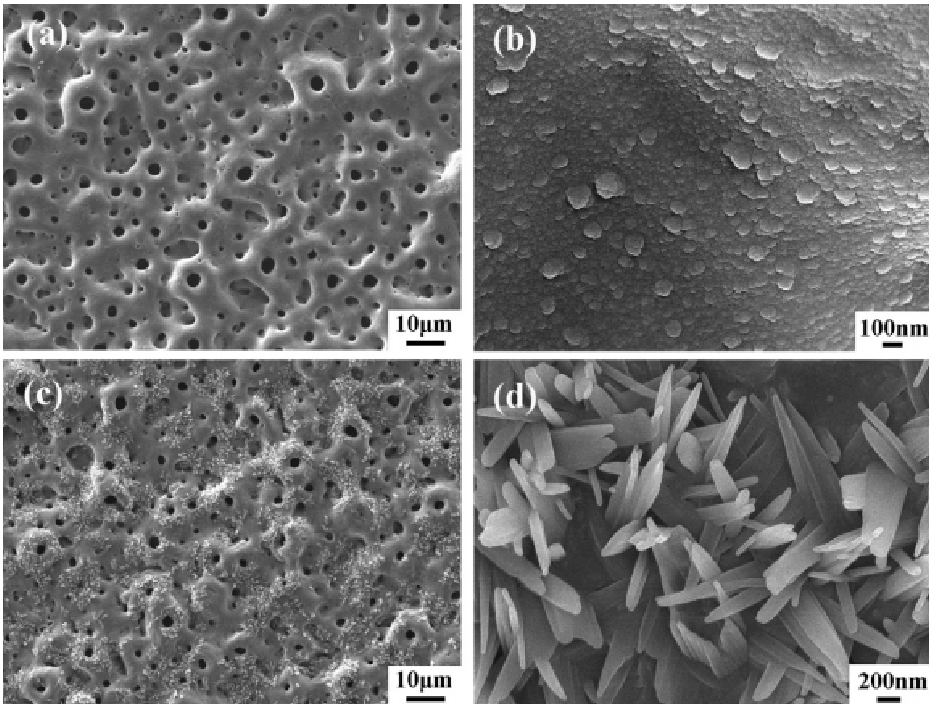

Figure 4. Surface morphologies of the TiO_2 (**a**,**b**) and $TiO_2/CaSiO_3$ (**c**,**d**) coatings in different magnifications [37]. Reprinted with permission from reference [37] 2013 Elsevier.

From the above, it can be seen that titanium alloy micro-arc oxidation bioactive coating has highly bonding strength with the matrix due to the compact interior. In addition, the loose and porous outer layer, which are conducive to protein adsorption, osteoblast adhesion and bone tissue regeneration, promote bone integration and prevent implant-related infections. It is the direction of further exploration to regulate the bioactive components and construct multi-level micro- and nano-structure coating for cell adhesion and proliferation. Additionally, in order to prevent from inflammation that would affect healing and further promote tissue repair, the construction of multi-functional coatings with biological activity and bacteriostasis are a hot research topic [39].

2.2. *Plasma Spraying*

Plasma spraying technique, as a practical and reliable coating method, has been carried out for decades. It is worthy of note that plasma-spray technique has attracted lots of attention for biomedical field, due to the advantages of low cost, high efficiency and ability to control the coating thickness [40]. During processing, numerous variables affect the final performance of ceramic coating, such as chemical compositions, structures, and crystallinity [41,42]. The schematic diagram of the plasma spray equipment is shown in Figure 5. It can be seen the system comprises DC electrical power source, gas flow control, water-cooling system and powder feeder [43].

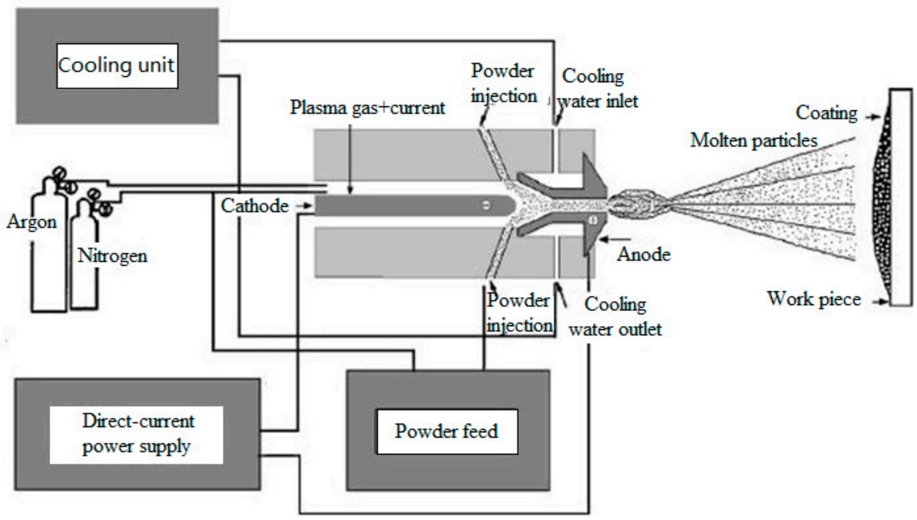

Figure 5. Schematic diagram of plasma spraying [43]. Reprinted with permission from reference [43] 2012 Elsevier.

Recently, with the progresses in the utilization of titanium devices coating, plasma sprayed ceramic coatings not only achieve most mechanical requirements, but also provide suitable growth environment for bone cells and tissues [44]. It was reported that plasma sprayed ceramic coatings are able to increase performances in bonding strength, hardness, wear and corrosion resistance, etc. There is no doubt that the improvements of bioceramic coating are mainly related to thermal stability, phase and chemical composition, as well as microstructure [45]. Plasma sprayed bi-layer coating containing Al_2O_3–13 wt.% TiO_2 and ZrO_2 layer was successfully deposited on Ti–13Nb–13Zr substrate, and the corrosion and wear resistance properties of the coatings were significantly increased due to its lower porosity and higher adhesion strength [46,47]. In addition to composition design of bioactive coatings, heat treatment after plasma spraying might affect the mechanical properties [48].

For plasma sprayed coatings in biomedical implants, hydroxyapatite (HA)-based coatings seem to be the most widely used in surface modification, resulting from HA can lead to favorable biocompatibility and bone regeneration between the bone tissue and implant surface [49]. In order to improve the biological stability of HA-coated implants for long-term, Yang et al. [50] found industrial pure titanium can be used as an effective bonding agent to significantly improve the interface bonding and stress reduction of the plasma-sprayed HA coating and Ti-alloy system. As is shown in Figure 6, the excellent bonding can be observed between commercial pure titanium (CP-Ti) and the substrates, and the surface roughness of CP-Ti is unaltered after application of the HA coating. Furthermore, the corrosion resistance and cytocompatibility were enhanced by plasma sprayed HA and pure Ti coatings on Ti alloy matrix [51]. In another study, an innovative double-layer of HA/Al_2O_3-SiO_2 nanocomposites is deposited on the surface of titanium implants by plasma spray technique. The results indicated that bi-layer plasma sprayed coating enhanced roughness, wettability, as well as improved the cell viability and proliferation compared to single layer of HA coating [52]. Meanwhile, biofunctional (Mg, Sr)-HA coatings with high bonding strength were successfully produced by plasma-spray technique [53]. In Figure 7, cellular extensions and extracellular matrices secreted were observed, which demonstrated the HA composite coating with Mg and Sr ions have great biological activity. In addition to an HA coating, pure Ti coating obtained by plasma-spray technique on Poly-ether-ether-ketone substrate seems to be an effective way for surface modification [54,55].

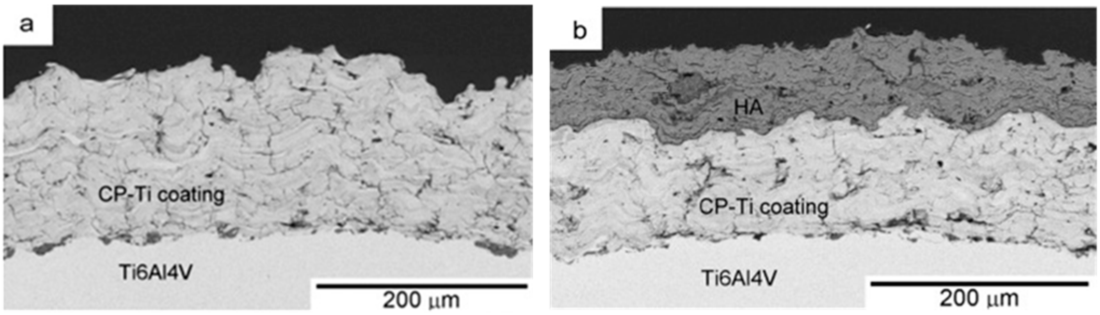

Figure 6. Cross-sectional electron backscatter diffraction (EBSD) images of the (**a**) CP-Ti and (**b**) HA coating on the CP-Ti [50]. Reprinted with permission from reference [50] 2013 Elsevier.

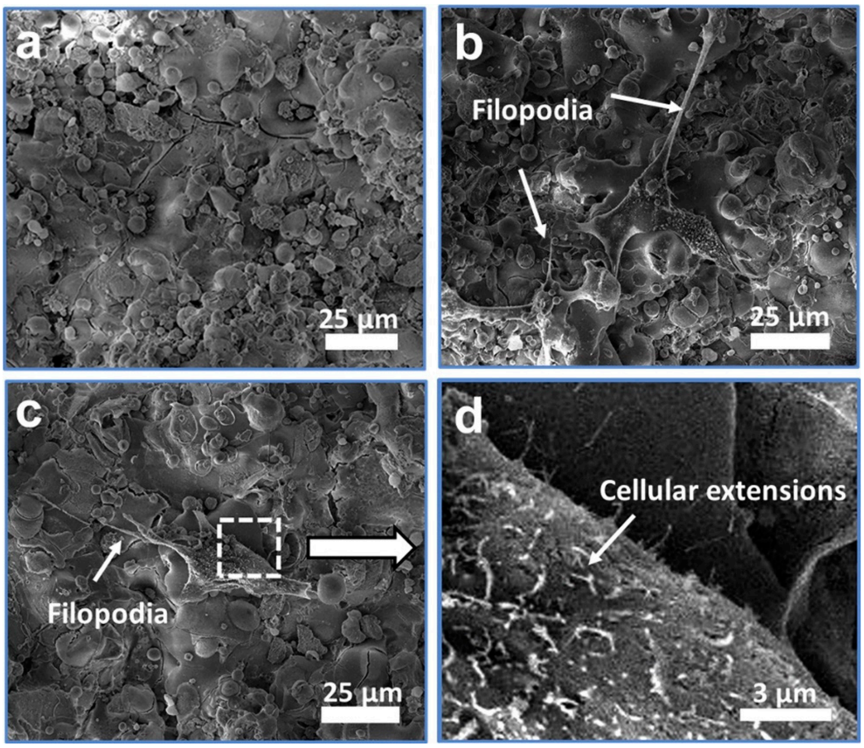

Figure 7. Micrographs of (**a**) the surface of the control group without cells and (**b**–**d**) cell morphology after culture on the (Mg, Sr)-HA coatings for five days. White arrows show filopodia of cells and cellular extensions. A large magnification (**d**) of the white dash box in (**c**) shows the cellular extensions [53]. Reprinted with permission from reference [53] 2018 Elsevier.

In recent years, several concerns have been raised on stress shielding, poor osseointegration, composition control, porosity and low adhesive strength of the coating is an immense challenge, which influences the long-term stability of implants. To further improve the surface comprehensive properties of implants, it is necessary to combine various surface modification technologies to produce biofunctional coatings with excellent mechanical properties. In line with what Ke et al. [56] reported, a gradient HA-based composite coating with antibacterial properties was deposited utilizing laser and plasma spray technology for enhancing the mechanical properties.

2.3. Ion Implantation

While numerous techniques were used to modify implant material surfaces, ion implantation has attracted wide attention for biomedical applications resulting from mechanical and electrochemical properties of metal materials treated with ion implantation have been shown to significantly improve [57,58]. Particularly, it's an effective way to enhance the anchoring strength of coating on substrate without altering the original characteristics of the matrix material. Additionally, ion implantation is a promising strategy to prevent infection and improve implant osseointegration for biological systems [59]. In general, ion implantation technology can be divided into two categories: ion beam ion implantation (IBII) and plasma immersion ion implantation (PIII). These two methods are different in the way of producing high energy ions, but the physical mechanism of surface modification is similar. In the ion implantation process, energetic ions, whose energy is closely related to penetration depth inside the substrate, get incorporated into the substrate after losing all their energies [60].

Recently studies have found that PIII has attracted wide attention for biomedical applications due to PIII technique enables to inject various elements into the near-surface with a complex shape of various substrates [61]. As is shown in Figure 8, silver nanoparticles were successfully implanted on the hierarchical titanium surface by PIII, and the rough surface is obtained by virtue of acid etching [62]. Furthermore, the content and distribution of implanted ions in the matrix can be precisely controlled using PIII technology by adjusting the implantation parameters [63–65]. Additionally, surface micromorphology, which is associated with the incident current of PIII, would influence the corrosion resistance, Young's modulus, nano-hardness and bioactive of cells in NiTi alloys surface, as reported by Li et al. [63]. Previous studies have shown that the implantation of zinc ions on titanium surface by PIII technology can provide an environment with great antimicrobial and biocompatibility [64]. According to Jin et al. [65], Zn ions were implanted into the oxalic acid etched titanium using PIII technology. The Zn-implanted titanium not only had an antibacterial effect, but also promotes osseointegration while without negative side effect by controlling the content and release of Zn ions.

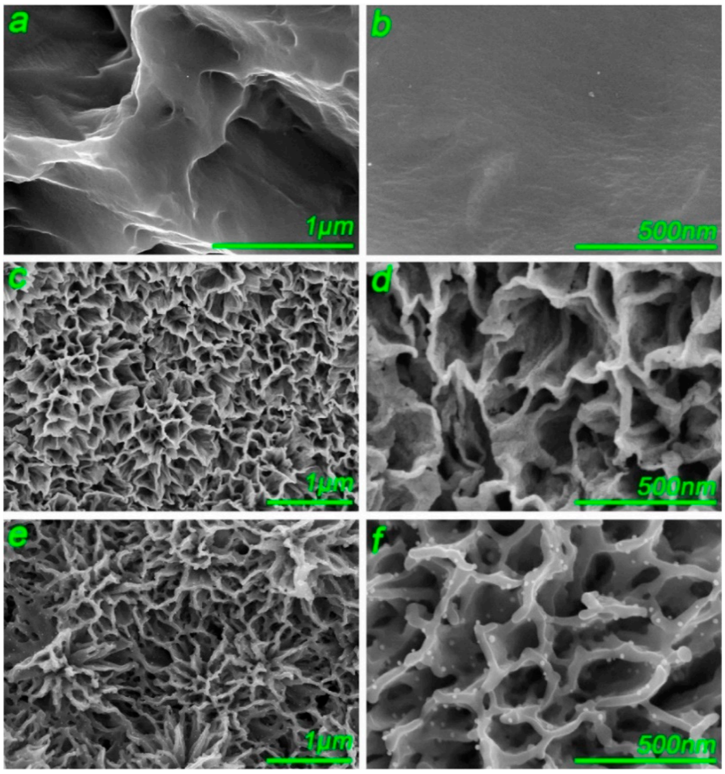

Figure 8. Surface morphology of the designed samples micro-Ti (**a**,**b**), nano-Ti (**c**,**d**) and Ag-Ti (**e**,**f**) [62]. Reprinted with permission from reference [62] 2016 Elsevier.

There are numerous elements, such as zinc (Zn), silver (Ag), fluorine (F), tantalum (Ta), calcium (Ca), chlorine (Cl),nitrogen (N), iodine (I), copper (Cu) and carbon (C), that might be injected into titanium alloys surface by PIII of the corresponding ions [66–68]. Notably, these ions can divide into metal ions and non-metal ions to achieve a variety of surface functions. Recent studies have pointed that a significant enhancement of surface mechanical properties and the corrosion resistance have been observed by implanting C ions with the PIII technique [66]. Furthermore, the nitrogen ion implanted the surface of Ti-35Nb-7Zr-5Ta β titanium alloy and found that the specimens have better corrosion resistance and more secure ions release rate than the unmodified alloy [67]. Additionally, ion implantation, as a promising approach, endows the surface of titanium alloys with antimicrobial effect by incorporating with ions such as Zn, Cu, Ag and F ions. There is no doubt ions' gradual release from specimens into surrounding tissues affect the bactericidal and cell activity, which would elicit a favorable cells response from tissues [68]. Thus, an emerging research area is the development of anti-bacterial implant materials. For example, Kim et al. [69] indicated the concentration of implanted silver and the topography of the surface determine the effect on the action against micro-organisms. As is shown in Figure 9, hierarchical titanium with silver nanoparticles surface (Figure 8e,f) significantly promoted cellular adhesion and proliferation while have excellent antimicrobial ability.

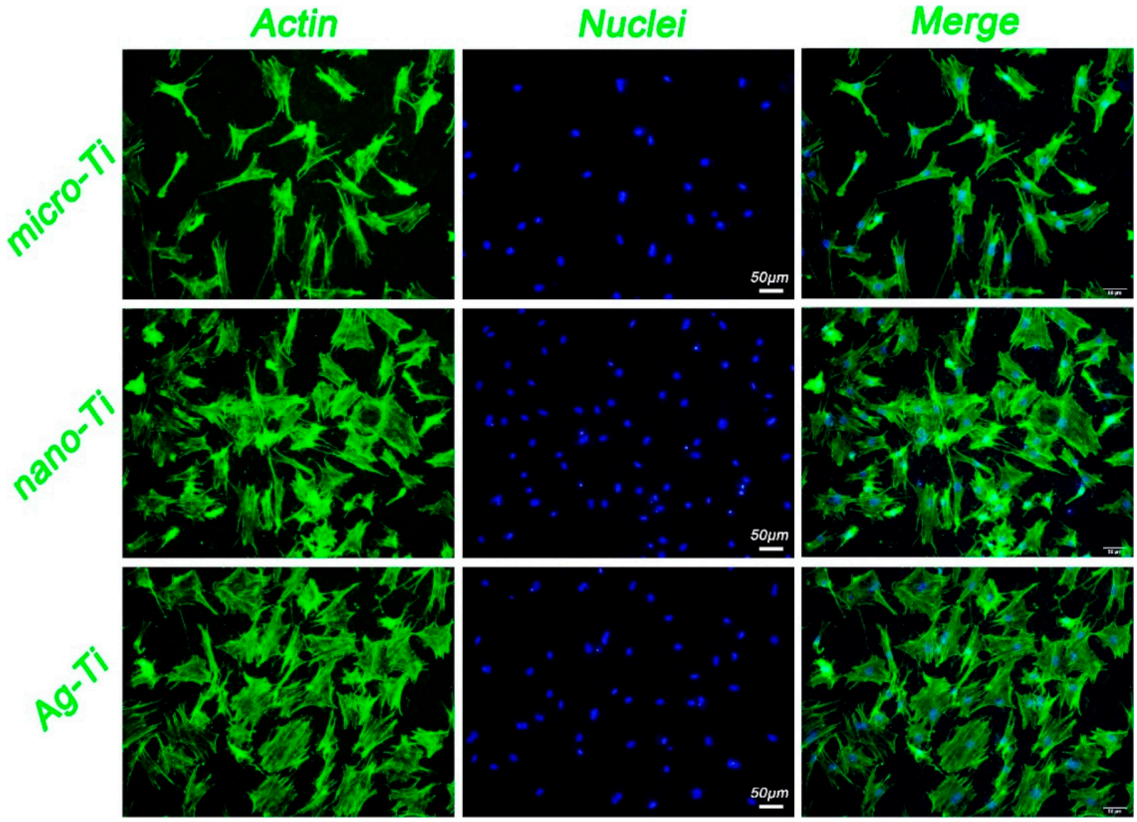

Figure 9. Investigation of the initial adhesion and spreading behaviors of mesenchymal stem cells (MSCs) after 24 h of culture on the samples micro-Ti, nano-Ti and Ag-Ti. Note: actin, green; nuclei, blue [62]. Reprinted with permission from reference [62] 2016 Elsevier.

As one of the most important methods for surface modification of titanium, ion implantation is convenient, controllable and flexible. Implantation of ions with various functions can not only effectively improve the physical and chemical properties or biological activities of titanium alloys, but also improve the antimicrobial ability of titanium alloys. These are closely related to the success rate of implants. However, single ion implantation modification only improves some properties of implanted materials. In recent years, with the development of composite ions implantation technology, the development trend of ion implantation technology of titanium materials will be to obtain multi-functional surface by simultaneously implanting various ions.

2.4. Laser Surface Modification

Laser surface modification technology, which uses laser as a heat source to modify the surface of metal materials, has gained traction in recent years. The main advantages are that it can control accuracy and features of implant surface while being highly efficient, pollution-free and have low material consumption [70,71]. Laser can not only be used to prepare periodic micro/nano structures on most material surfaces with various surface geometries, such as dimple, linear, rippled patterns and so on, but also change phase structure and chemical composition of the surface by cladding bioactive materials on substrate [72–74]. Researchers have attempted to find a biocompatible surface morphology to improve osteointegration and tissue regeneration, which is critical for the life, durability and uninterrupted functionality of implants in vivo inthe early phase of implantation [75,76].

Depending on the feature to be manufactured and material types, various lasers with unique functions are used, such as femtosecond lasers, excimer laser (Nd:YAG), etc. [71]. Previous studies have revealed that using femtosecond lasers to form a periodic structure can control the proliferation of cells [77]. Laser-induced periodic surface structures (LIPSSs), nanopillar-(NPs) and microcolumn-(F) textured surfaces were produced by femtosecond laser treatment on Ti-6Al-4V alloy substrate (Figure 10) [78,79]. LIPSSs and NPs can improve osteoblastic differentiation of stem cells, as demonstrated by Cunha et al. [78]. Recently, it was significantly observed by Bryane et al. [79] that submicron surface structures with various periodic ripples were produced on titanium substrate by pulsed femtosecond lasers, and cell metabolism of laser ablation surface was higher than the control surfaces.

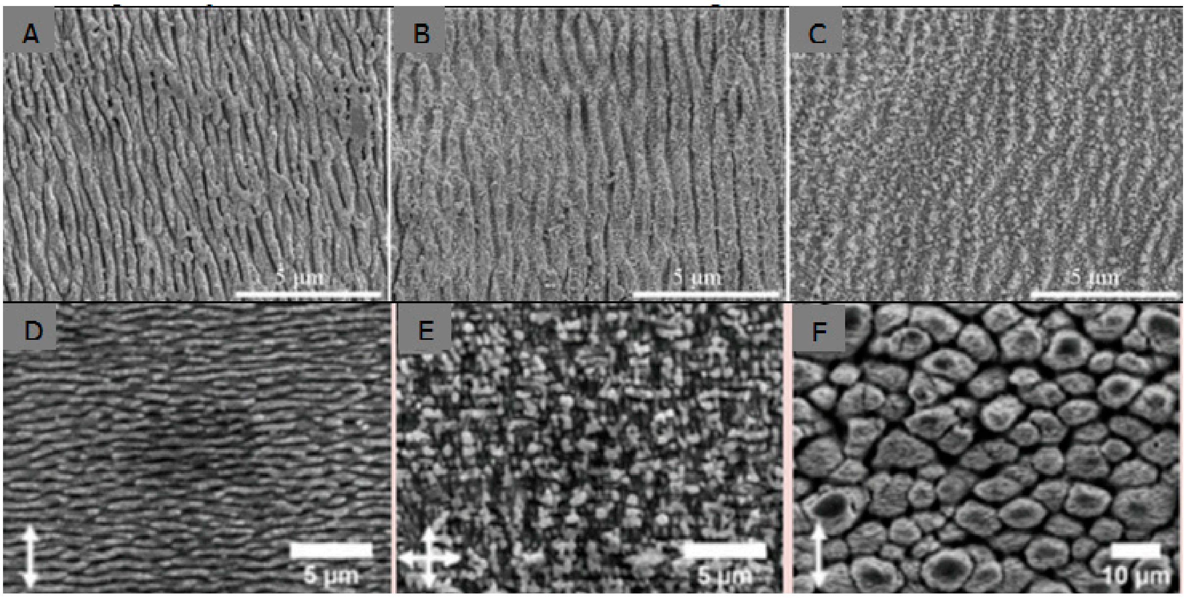

Figure 10. SEM micrographs of laser-induced periodic ripples surface structures (**A**–**D**), nanopillar (**E**) and microcolumn (**F**) textured surfaces [78,79]. Reprinted with permission from reference [78] 2015 Elsevier.

In addition to femtosecond lasers, researchers have also explored the surface modification behavior of other lasers by controlling machining parameters. Marticorena et al. [80] showed that laser irradiation of pure titanium films with different pulse frequencies produces surface structures with different morphologies. Experimental results show that the surface microstructure, texture and roughness of implant surfaces are important for the biocompatibility of implants in vivo. Additionally, Trtica et al. [81] found that liquid (water) is the preferred medium for the surface structure of titanium alloy implants. At the same time, water also showed high oxidation capacity, which promotes the surface biological activity. Hsiao et al. [82] developed an efficient method to increase surface roughness in titanium alloy (Ti-6Al-4V) with a low energy pulsed ultraviolet (UV) laser, which was similar to laser modified surfaces. Renu et al. [83] presented laser surface texturing of titanium alloy (Ti-6Al-4V) with line and dimple geometry using ArF excimer laser. After laser modification, Young's modulus, corrosion resistance and nano-hardness increase as compared with the as-received titanium. The fluorescence micrograph showed that the surface morphology controls cell adsorption and growth direction, as shown in the Figure 11.

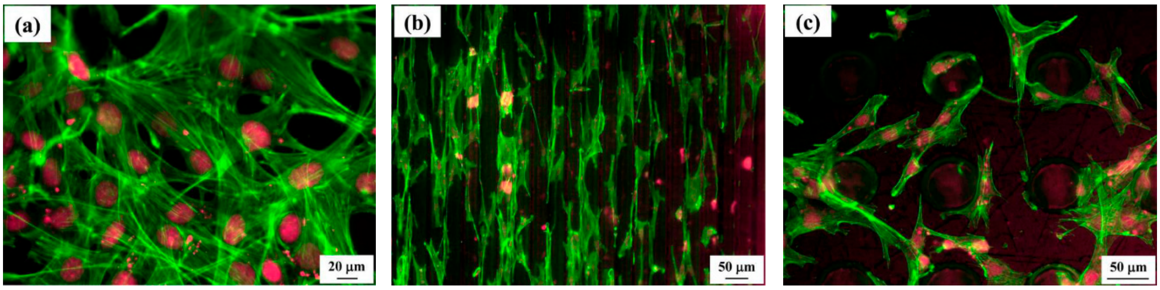

Figure 11. Micrographs of (**a**) as received and laser surface textured with (**b**) line geometry and (**c**) dimple geometry showing the attachment of MC3T3-E1 mouse fibroblast cell on the surface [83]. Reprinted with permission from reference [83] 2015 Elsevier.

In order to overcome the problem of the constituent metals leach from the implant, which may be at risk of biotoxicity, and further improve biocompatibility and bioactivity, researchers have proposed laser coating bioactive coating on the surface of implants [84,85]. Figure 12 shows the principle of laser cladding (LC) that the high-energy laser beam melts the material and then directly coats it on the target surface and merges with it. Furthermore, as a flexible technology, we can obtain multifunctional coatings by changing the composition of power.

A great amount of researchers have focused on exploring the effect of morphology and composition of bioceramics surface on implants. The mechanical properties and biological responses of the coatings can be controlled accurately by biomimetic design of the roughness and graded porosity of the coatings without affecting the chemical structure of the matrix [86,87]. In this case, calcium phosphate coatings with different morphologies by changing the pulse frequency were obtained, as reported by Paital et al. [88]. After treatment, the hydrophilicity of the samples is enhanced, which improved the proliferation and diffusion ability of the cell. According to Zheng et al. [89], the bioceramic coatings were prepared on Ti-6Al-4V by LC. Simulated body fluids (SBF) results show that the appearance of flake-like and cotton-like morphology of apatite provides favorable conditions for osseoconnection. In addition, the multifunctional design of implants is closely related to the composite coating, and coupled with appropriate post-treatment, which can further affects the biomedical application of implants. Rasmi et al. [90] used LC to prepare functionally graded material (FGM) HA-TiO_2, which comprises of five different preplaced layers on Ti-6Al-4V alloy. Figure 13 indicates that the interface thickness between the composite coating and the substrate is higher, and cellular structure was observed in the upper part of CL. Apparently, the FGM with multiphase, micro-textured coating provides better metallurgical bonding at the interface, and the wettability and the protein adsorption capacity of FGM are significantly improved.

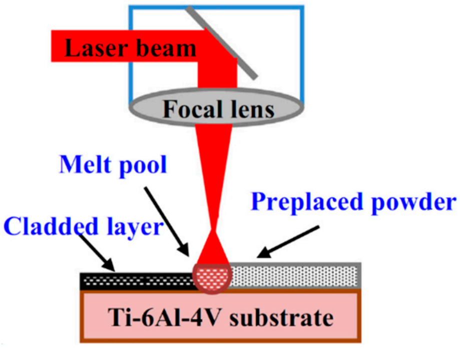

Figure 12. Laser cladding (LC) schematic diagram [90]. Reprinted with permission from reference [90] 2018 Elsevier.

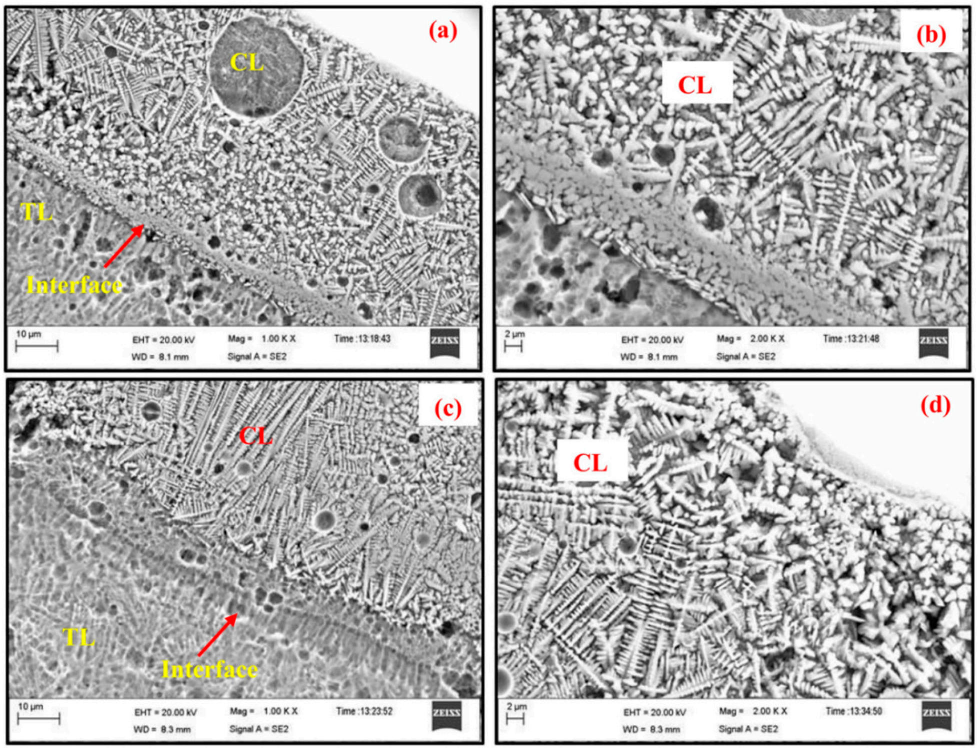

Figure 13. Cross-sectional morphology of 100% HA and functionally graded material (FGM) laser cladding at laser energy density (LED) 21.6 J/mm^2 (**a**,**c**) interface between the crust layer (CL) and the transition layer (TL) (low magnification) and (**b**,**d**) CL (high magnification) [90]. The top layer of cladding is identified as CL. Beneath the CL, the TL is present, where transition of elements between cladding and substrate occurs. Reprinted with permission from reference [90] 2018 Elsevier.

The composite material composed of bioceramics and metal can not only improve the mechanical properties of implant surface, but also affect the chemical properties such as biocompatibility [91,92]. MgO doped Ta coatings are successfully created by high power lasers on CP-Ti substrate. With the addition of MgO, the hardness of the coating is four times higher compared to CP-Ti. Additionally, the biocompatibility and cells proliferation was further improved by incorporating MgO in the Ta coatings [91]. In studies by Deng et al. [92], LC was used to create a compositional gradient NiTi/HA coatings on NiTi substrate, as well as sintered NiTi (sNiTi)/HA-acid coating which is obtained by acid-etching post-treatment. Figure 14 shows that by coating NiTi with HA the biocompatibility of NiTi implants was further enhanced. An increase in extracellular matrix generation and mineral deposition of osteoblasts was seen on sNiTi, sNiTi/HA and sNiTi/HA-acid coatings. In particular, the presence of HA significantly promoted the proliferation of osteoblasts.

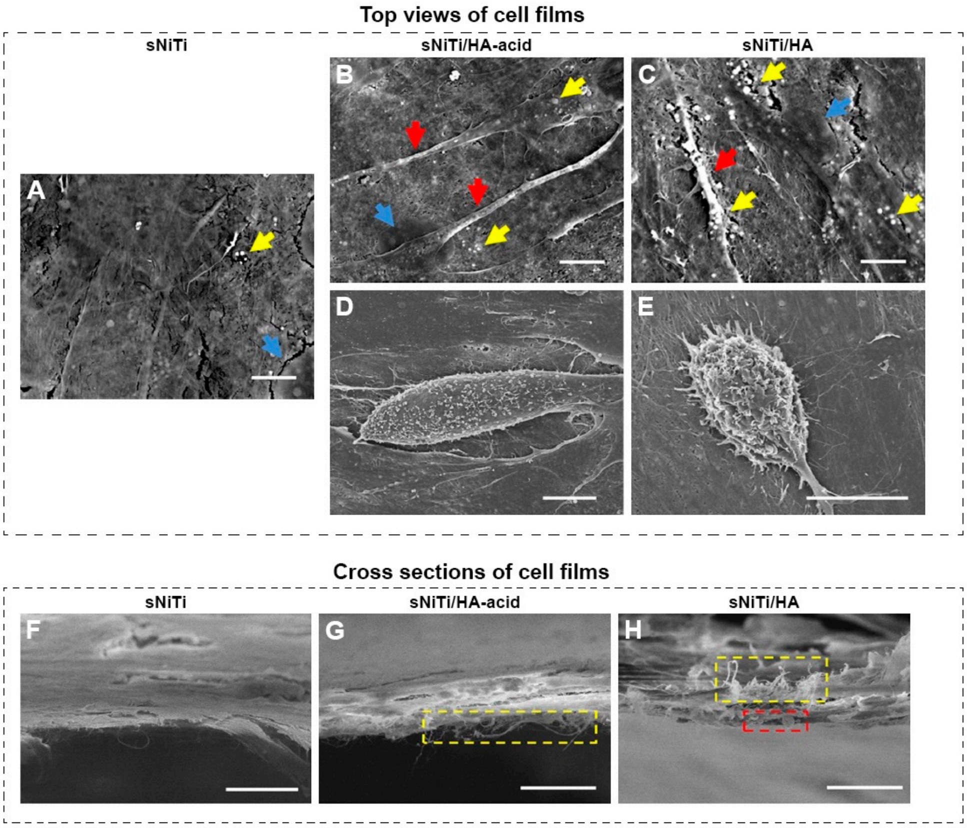

Figure 14. Osteoblast morphology on different sNiTi plates [92].After three days of osteoblast culture, the top view of the cell monolayers was imaged by SEM: (**A**) sNiTi; (**B**) and (**D**) sNiTi/HA-acid; (**C**) and (**E**) sNiTi/HA. Representative areas in (**A**–**C**) showing mineral deposits (yellow arrows), cell nuclei (blue arrows), and lamellipodia (red arrows). Some cells displayed a dome shape on sNiTi/HA-acid, as in (**D**); and sNiTi/HA, as in (**E**); no similar cells were found for sNiTi. Cross sections of the osteoblast monolayer were also imaged: (**F**) sNiTi; (**G**) sNiTi/ HA-acid; (**H**) sNiTi/HA. A fibrous structure which is highlighted by yellow rectangles was observed in (**G**,**H**) and possibly represents extracellular matrix. The red rectangle in (**H**) indicates possible mineralized microspheres attached to the cell monolayer. Scale bar: 10 µm. Reprinted with permission from reference [92] 2018 Elsevier.

During the implantation process, the applied stress may exceed the coating-substrate adhesion strength, which causes the separation of the coating from the metal surface, thereby impairing its function of promoting bone integration [93]. Therefore, Miranda et al. [94] proposed a novel integrated approach to avoid the detachment of HA coatings during implantation and affecting biological activity. As explained by the schematic diagram as seen in Figure 15, the holes on the surface of Ti6-Al-4V are processed by Nd:YAG laser, and then filled with HA by laser sintering.

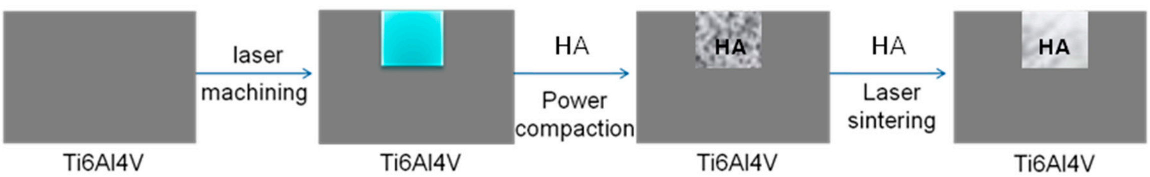

Figure 15. Schematic representation of the experimental procedure used to produce laser sintered Ti6Al4V doped HA structures [94]. Reprinted with permission from reference [94] 2019 Elsevier.

It can be seen from the above that the energy density, wavelength width, scanning speed, pulse frequency and surface texture design of the laser will affect the biomechanical properties of the final surface. Laser cladding is a flexible and effective method, by mixing different powder materials, forming a special biological coating on the surface of parts, so as to obtain the desired properties. However, due to the inconsistency between the thermal expansion coefficient of the cladding layer and the matrix, surface quality problems, such as cracks and pores that maybe difficult to control precisely in the cladding layer.

2.5. Sol-Gel

Sol-gel technology is a versatile chemical synthesis technology that has been developed recently relates to hybrid materials which can be used to achieve unusual composite properties [95,96]. To some extent, the application of sol-gel method can produce excellent coating owing to its advantages properties such as low process temperature, facile and inexpensive preparation [97]. The process illustrated in Figure 16 is not really complete. In fact, altering the initial precursors, time allowed for gelation, catalysts, degree of solvation, gelation conditions or physical processing of the gel itself can control the coating performance [96].

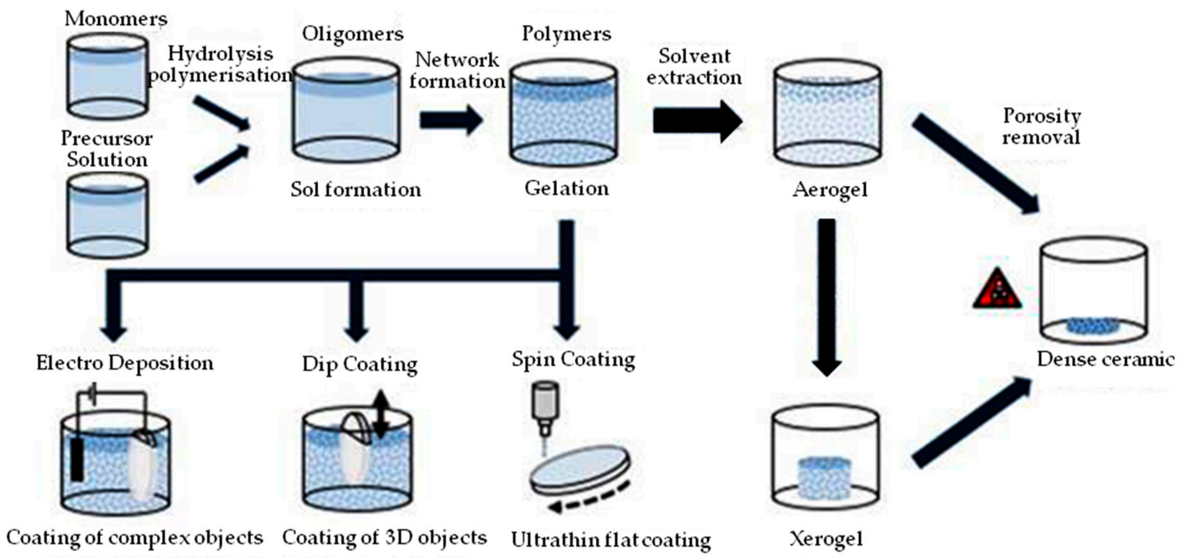

Figure 16. Gel synthesis routes. Processes are defined as sol–gel by the transition of colloidal solution to an interconnected gel network (gelation). The further processing stages illustrated are non-redundant and may be combined depending on the specific needs of the application [96]. 3D: three-dimensional. Reprinted with permission from reference [96] 2016 Elsevier.

Recently, Çomakl et al. [98] indicted that a titanium dioxide thin film structure prepared by the sol-gel on CP-Ti substrate is more stable and thicker in comparison to the continuous ion layer adsorption and reaction (SILAR) method, and the wear properties and corrosion resistance is enhanced. The surface morphology of sol-gel and SILAR samples is shown in Figure 17. Moreover, sol-gel method can also be combined with a variety of coating technologies and can produce ideal biological coating by selecting the appropriate conditions [99,100]. Anjaneyulu et al. [101] prepared sol–gel-derived HA coatings via spin coating on Ti-6Al-4V alloy substrates. The sol–gel-derived HA surface has excellent corrosion resistance and great cellular response in terms of cell attachment, growth and proliferation. Since the loose particles on the medical implant may cause cancer and inflammation, the coating needs to be firmly bonded to the implant.

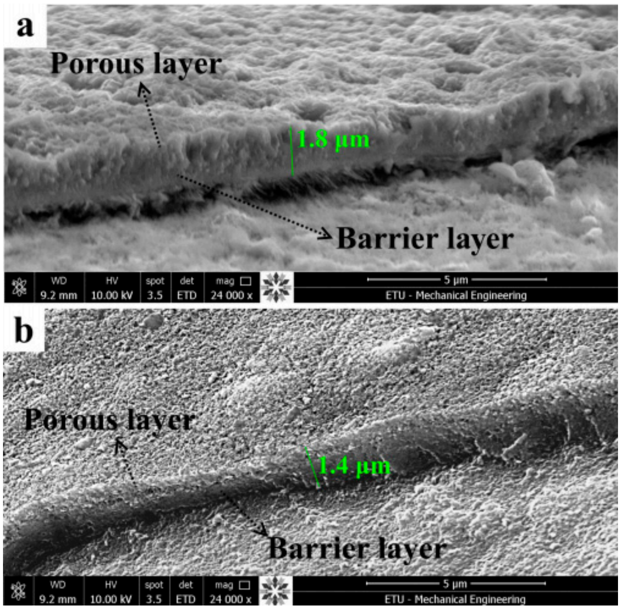

Figure 17. Cross-section SEM micrographs of (**a**) sol-gel and (**b**) SILAR samples [98]. Reprinted with permission from reference [98] 2018 Elsevier.

Andrew et al. [102] improved the bonding strength and optimized the mechanical properties of the sol-gel coating by controlling the annealing temperature. In addition, researchers have found that the pretreatment of the precursor had a significant effect on the adsorption strength and mechanical properties of the coating [103]. Roest et al. [104] found that anodizing treatments could improve the adhesive bonding of HA on Ti substrates, especially for titanium alloys. Analogously, a dense and stable SiO_2 coating was deposited on the surface of pre-oxidized TiNi alloy by sol-gel method. This way improves the bonding strength between the substrate and film and corrosion resistance. Additionally, the release of Ni ions can be effectively prevented to ensure the biocompatibility of the implant, as reported by Yang et al. [105].

Sol-gel coating can not only act as a barrier layer to isolate the metallic substrates from the human body environment, but also achieve multi-functional coating by adding different components, such as corrosion inhibitors, growth factor and antibacterial factor [106]. Michelina et al. [107] prepared organic-inorganic composite coatings on the surface of CP Ti grade 4 substrates by sol-gel method, and successfully improved the elastic-plastic coating without cracks by adding poly (ε-caprolactide). Furthermore, on a cellular level, the implants had excellent bioactive and biocompatibility.

Sol-gel technology is an interesting way to modify the surface of the implants. The sol-gel technology is essentially the use of various materials that are controlled at processing media level, instead of raw materials in traditional processes that are neither geometrically controlled and chemically controlled or only geometrically controlled. With no doubt, combined with the change of coating preparation process and adding other functional components, different functional coatings can be obtained. In addition, how to shorten the processing time and improve the binding energy between the surface and the matrix by changing the processing parameters seems to be the main research direction at present.

2.6. Friction Stir Processing

Friction stir processing (FSP), heat source of processing is friction heat and plastic deformation heat, is a new method applied to surface repair. For the biomedical field, it is mainly used to modify surface microstructure or fabricate a composite layer on the surface of substrate. In particular, composite coatings produced by FSP not only can improve surface properties such as hardness, abrasion resistance, ductility, corrosion resistance, fatigue life and frictional properties, but also obtain desired multifunctional biomedical coating without or less affecting the matrix properties of the material [108–110].

FSP is one of the prospective surface modification technologies that allows to control mechanical properties by changing localized microstructure in a surface layer while retaining properties of the base material. In general, the final microstructure of FSP surface is dependent on several independent factors, such as processing parameters, chemical composition of modified material and consequent heat treatment [111]. As a fairly environmentally friendly process, FSP is used for uniform distribution of composition and microstructure, fabrication of ultra-fine grained materials and elimination of casting defects [112]. As reported in recently work, FSP was employed to obtain defect-free and homogenous fine-grained surface layer of the Ti-6Al-4V alloy by the applied processing parameters. The ultra-refined α phase or Martensite-α′ phase produced by phase transformation provides a beneficial condition for the enhancement in hardness and dry sliding wear performance [113]. In order to further optimize mechanical properties for biomedical applications, Wang et al. [114] systematically studied the microstructure evolution of Ti-35Nb-2Ta-3Zr alloy surface by FSP. As is shown in Figure 18, the size of equiaxed grains is considerably refined by the severe shear deformation in stir zone. Moreover, it is apparent that the occurrence of dynamic recrystallization is accompanied by phase transition due to severe plastic deformation during three-pass FSP.

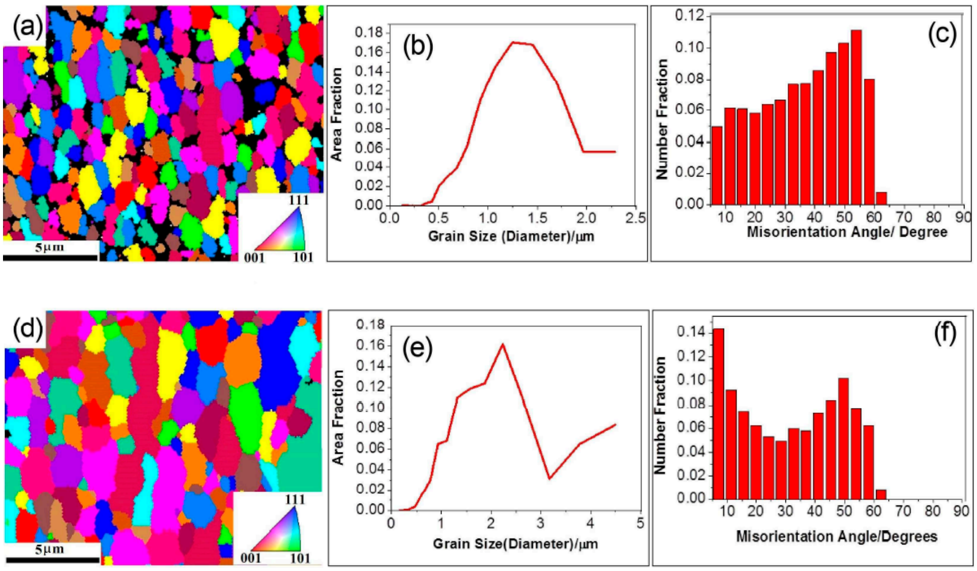

Figure 18. EBSD maps of equiaxed grains for three-pass friction stir processing (FSP)-processed sample at a rotational speed of 300 r/min: (**a**) orientation map, (**b**) distribution of grain size and (**c**) misorientation angle distribution in stir zone (SZ), and (**d**) orientation map, (**e**) distribution of grain size and (**f**) misorientation angle distribution in transition zone (TZ) [114]. Reprinted with permission from reference [114] 2017 Elsevier.

Numerous studies have demonstrated that FSP is an effective method of fabricating surface composites [115,116]. The common method with reinforcement particles in the fabrication of surface composites by holes is explained in Figure 19 [117]. In the first step, the holes with proper dimensions are machined on the modified plat and the reinforcement particles are filled in the holes. Then, the tool with probe is applied to pack the holes completely. It should be noted that dimension, shape and number of holes and distance between each other can be varied to achieve required volume fraction of the second phases. In general, when a reinforcing phase is incorporated into a matrix, surface composites show the synergistic effect of grain refinement by FSP and reinforcement particle [118,119].

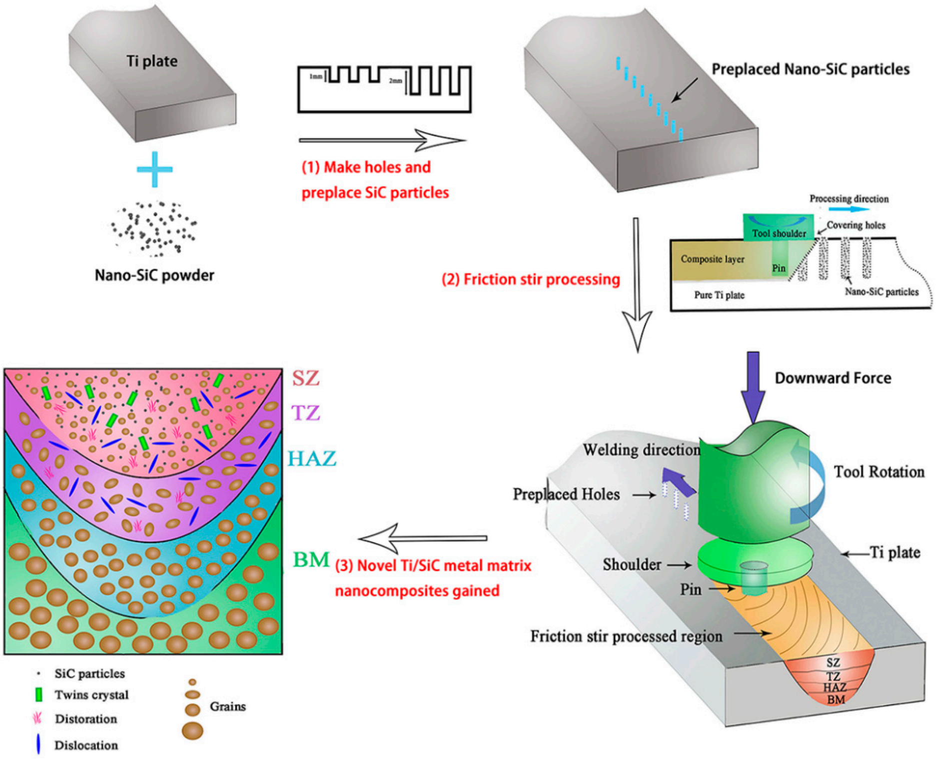

Figure 19. Schematic illustration of the process of producing the FSP-modified Ti/SiC metal matrix nano-composite (MMNC) [117].

Targeting on tissue-substrate interactions, several works has been done to explore the effects of FSP surface composites on titanium alloys for medical implant. Recently, FSP titanium alloys reinforced by HA, TiC, SiC and TiO_2 nano-particles are suitable for biomedical application [120]. Zhu et al. [117] successfully utilized FSP to fabricate titanium/silicon carbide composite layer on the surface of pure Ti substrate and found an increase of microhardness. Furthermore, the adhesion, proliferation and osteogenic differentiation of the cells on the surface of the nanocomposite material were enhanced. Then, TiO_2/TC4 composite coating, which provides a no biotoxicity environment for cells and promotes cell adhesion and proliferation, was produced [121]. Wang et al. [122] produced a promising biomaterial−TC4/Ag metal matrix nanocomposite, which can achieve a balance between the antibacterial effect and biocompatibility. In Figure 20, with the increase of silver content, the number of *staphylococcus aureus* (*S. aureus*) cells decreased significantly and dead cells with an indistinct or deformed membrane were observed on 2 mm-Ag-FSP.

This section mainly focused on introducing all the aspects and biomedical applications of FSP that is a novel and advanced solid-state surface modification technology, as well as reviewing the reported short literature on this subject. On the one hand, it is effective to refine the grain structure and eliminate surface defects during FSP because of dynamic recrystallization phenomena that occur in severe thermal deformation [123,124]. On the other hand, recent studies pertaining to coating pointed out that FSP has great potential to obtain functional gradient multifunctional composite coating from powder pre-placed sheet system by using different lengths of grooves and tools. However, the inferior flexibility of FSP limits its usage. This limitation restricts the use of the FSP technique to manufacture complex counterparts with precise dimensional tolerance as compared to the other fusion-based technology.

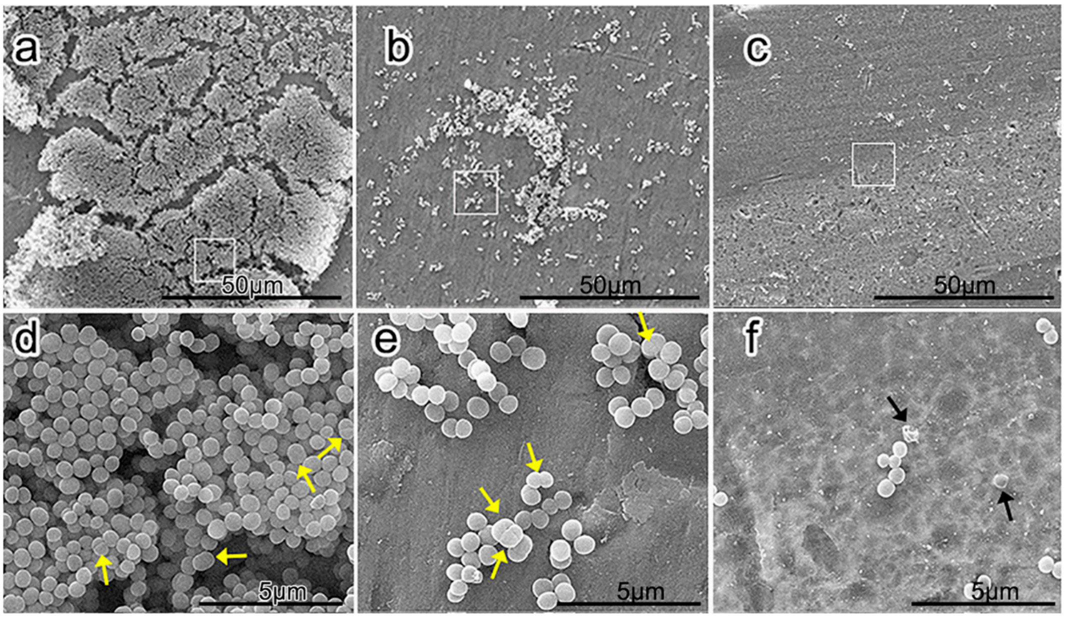

Figure 20. SEM images of *S. aureus* cells introduced on sample surfaces; (**a**–**c**) are TC4, 0 mm-FSP, and 2 mm-Ag-FSP at low magnification, respectively, and (**d**–**f**) are highly magnified images. Yellow arrows show cell fission, whereas black arrows show dead cells with an indistinct or deformed membrane [122]. Reprinted with permission from reference [122] 2018 Elsevier.

3. Conclusions

The surface modification of biomaterials has become a vital topic, especially in overcoming the rejection reactions, such as inflammation and allergic reactions. When these biomaterials are implanted into the body, most of them will interact with the maternal environment, which cannot achieve the desired effect. Thus far, surface modification of biomaterials is believed to be the best way to improve its various properties. This paper summarizes the methods and research progress of biomedical surface modification in recent years.

This review provides a summary of the commonly emphasized surface modification methods, such as plasma spraying, ion implantation, micro-arc oxidation, laser surface modification, sol-gel and FSP. These methods are of great help to the practical application of biomedical implants; however, there are still some deficiencies. In order to improve the success rate of implants and achieve long-term stability of implants, it is necessary to combine surface modification and biomedicine to design the optimal surface morphology and formulate effective coating immobilization strategies.

Funding: The authors would like to acknowledge the financial support provided by National Science Foundation under Grant Nos. 51674167, 51831011, 51302168, 51874225, 51671152.

Acknowledgments: The authors sincerely thank Qingge Wang and Haibo Wu from Xi'an University of Architecture and Technology for data analysis of this paper.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Kurtz, S.; Mowat, F.; Ong, K. Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. *J. Bone Jt. Surg. Am.* **2007**, *89*, 780–785.
2. Barrere, F.; Mahmood, T.; De Groot, K.; Van Blitterswijk, C.; Van Blitterswijk, C. Advanced biomaterials for skeletal tissue regeneration: Instructive and smart functions. *Mater. Sci. Eng. R Rep.* **2008**, *59*, 38–71. [CrossRef]
3. Zethraeus, N.; Borgström, F.; Ström, O. Cost-effectiveness of the treatment and prevention of osteoporosis—A review of the literature and a reference model. *Osteoporos. Int.* **2007**, *18*, 9–23. [CrossRef]

4. Singh, R.; Singh, S.; Hashmi, M. Implant materials and their processing technologies. In *Reference Module in Materials Science and Materials Engineering*; Elsevier: Amsterdam, The Netherlands, 2016.
5. Rony, L.; Lancigu, R.; Hubert, L. Intraosseous metal implants in orthopedics: A review. *Morphologie* **2018**, *102*, 231–242. [CrossRef] [PubMed]
6. Rabadia, C.D.; Liu, Y.J.; Wang, L.; Sun, H.; Zhang, L.C. Laves phase precipitation in Ti-Zr-Fe-Cr alloys with high strength and large plasticity. *Mater. Des.* **2018**, *154*, 228–238. [CrossRef]
7. Wang, L.Q.; Lu, W.J.; Qin, J.N.; Zhang, F.; Zhang, D. Microstructure and mechanical properties of cold-rolled TiNbTaZr biomedical β titanium alloy. *Mater. Sci. Eng. A* **2008**, *490*, 421–426. [CrossRef]
8. Niespodziana, K.; Jurczyk, K.; Jakubowicz, J.; Jurczyk, M. Fabrication and properties of titanium–hydroxyapatite nanocomposites. *Mater. Chem. Phys.* **2010**, *123*, 160–165. [CrossRef]
9. Cao, H.; Liu, X. Activating titanium oxide coatings for orthopedic implants. *Surf. Coat. Technol.* **2013**, *233*, 57–64. [CrossRef]
10. Shariq, N.; Zohaib, K.B.D.S.; Sana, Z.B.D.S.; Muhammad, S.Z.B.D.S. Bioactivity and osseointegration of PEEK are inferior to those of titanium: A systematic review. *J. Oral Implantol.* **2016**, *42*, 512–516.
11. Noman, H.; Liu, S.F.; Lu, E.Y.; Wang, L.Q.; Liu, R.; Lu, W.J.; Zhang, L.C. Mechanical behavior and phase transformation of β-type Ti-35Nb-2Ta-3Zr alloy fabricated by 3D-Printing. *J. Alloy. Compd.* **2019**, *790*, 117–126.
12. Rabadia, C.D.; Liu, Y.J.; Jawed, S.F.; Wang, L.; Li, Y.H.; Zhang, X.H.; Sercombe, T.B.; Sun, H.; Zhang, L.C. Improved deformation behavior in Ti-Zr-Fe-Mn alloys comprising the C_{14} type Laves and β phases. *Mater. Des.* **2018**, *160*, 1059–1070. [CrossRef]
13. Chakraborty, R.; Shahid Raza, M.; Datta, S.; Saha, P. Synthesis and characterization of nickel free titanium–hydroxyapatite composite coating over Nitinol surface through in-situ laser cladding and alloying. *Surf. Coat. Technol.* **2019**, *358*, 539–550. [CrossRef]
14. Bosco, R.; Van Den Beucken, J.; Leeuwenburgh, S.; Jansen, J. Surface engineering for bone implants: A trend from passive to active surfaces. *Coatings* **2012**, *2*, 95–119. [CrossRef]
15. Aliasghari, S.; Skeldon, P.; Thompson, G. Plasma electrolytic oxidation of titanium in a phosphate/silicate electrolyte and tribological performance of the coatings. *Appl. Surf. Sci.* **2014**, *316*, 463–476. [CrossRef]
16. Çelik, I.; Alsaran, A.; Purcek, G. Effect of different surface oxidation treatments on structural, mechanical and tribological properties of ultrafine-grained titanium. *Surf. Coat. Technol.* **2014**, *258*, 842–848. [CrossRef]
17. Chu, H.J.; Liang, C.J.; Chen, C.H.; He, J.L. Optical emission spectroscopic determination of the optimum regions for micro-arc oxidation of titanium. *Surf. Coat. Technol.* **2017**, *325*, 166–173. [CrossRef]
18. Karbowniczek, J.; Muhaffel, F.; Cempura, G.; Cimenoglu, H.; Czyrska-Filemonowicz, A. Influence of electrolyte composition on microstructure, adhesion and bioactivity of micro-arc oxidation coatings produced on biomedical Ti6Al7Nb alloy. *Surf. Coat. Technol.* **2017**, *321*, 97–107. [CrossRef]
19. Ha, J.Y.; Tsutsumi, Y.; Doi, H.; Nomura, N.; Kim, K.H.; Hanawa, T. Enhancement of calcium phosphate formation on zirconium by micro-arc oxidation and chemical treatments. *Surf. Coat. Technol.* **2011**, *205*, 4948–4955. [CrossRef]
20. Rao, X.; Li, J.; Feng, X.; Chu, C.L. Bone-like apatite growth on controllable macroporous titanium scaffolds coated with microporous titania. *J. Mech. Behav. Biomed.* **2018**, *77*, 225–233. [CrossRef]
21. Yang, W.; Xu, D.; Wang, J.; Yao, X.; Chen, J. Microstructure and corrosion resistance of micro arc oxidation plus electrostatic powder spraying composite coating on magnesium alloy. *Corros. Sci.* **2018**, *136*, 174–179. [CrossRef]
22. Liu, S.M.; Li, B.; Liang, C.H.; Wang, H.S.; Qiao, Z.X. Formation mechanism and adhesive strength of a hydroxyapatite/TiO_2 composite coating on a titanium surface prepared by micro-arc oxidation. *Appl. Surf. Sci.* **2016**, *362*, 109–114. [CrossRef]
23. Li, L.H.; Kong, Y.M.; Kim, H.W.; Kim, W.Y.; Kim, H.E.; Heo, S.J.; Koak, J.Y. Improved biological performance of Ti implants due to surface modification by micro-arc oxidation. *Biomaterials* **2004**, *25*, 2867–2875. [CrossRef] [PubMed]
24. Zafar, M.S.; Farooq, I.; Awais, M.; Najeeb, S.; Khurshid, Z.; Zohaib, S. Chapter 11-Bioactive surface coatings for enhancing osseointegration of dental implants. In *Biomedical, Therapeutic and Clinical Applications of Bioactive Glasses*; Woodhead Publishing: Cambridge, UK, 2019; pp. 313–329.
25. Xu, L.; Wu, C.; Le, X.; Zhang, K.; Liu, C.; Ding, J.; Shi, X. Effect of oxidation time on cytocompatibility of ultrafine-grained pure Ti in micro-arc oxidation treatment. *Surf. Coat. Technol.* **2018**, *342*, 12–22. [CrossRef]

26. Santos-Coquillat, A.; Tenorio, R.G.; Mohedano, M.; Martinez-Campos, E.; Arrabal, R.; Matykina, E. Tailoring of antibacterial and osteogenic properties of Ti6Al4V by plasma electrolytic oxidation. *Appl. Surf. Sci.* **2018**, *454*, 157–172. [CrossRef]
27. Li, Y.; Wang, W.; Duan, J.; Qi, M. A super-hydrophilic coating with a macro/micro/nano triple hierarchical structure on titanium by two-step micro-arc oxidation treatment for biomedical applications. *Surf. Coat. Technol.* **2017**, *311*, 1–9. [CrossRef]
28. Wang, X.; Li, B.; Zhou, L.; Ma, J.; Zhang, X.; Li, H.; Liang, C.; Liu, S.; Wang, H. Influence of surface structures on biocompatibility of TiO_2/HA coatings prepared by MAO. *Mater. Chem. Phys.* **2018**, *215*, 339–345. [CrossRef]
29. Sedelnikova, M.; Komarova, E.; Sharkeev, Y.; Tolkacheva, T.; Khlusov, I.; Litvinova, L.; Yurova, K.; Shupletsova, V. Comparative investigations of structure and properties of micro-arc wollastonite-calcium phosphate coatings on titanium and zirconium-niobium alloy. *Bioact. Mater.* **2017**, *2*, 177–184. [CrossRef] [PubMed]
30. Wang, P.; Wu, T.; Peng, H.; Guo, X.Y. Effect of $NaAlO_2$ concentrations on the properties of micro-arc oxidation coatings on pure titanium. *Mater. Lett.* **2016**, *170*, 171–174.
31. Yang, W.; Xu, D.; Guo, Q.; Chen, T.; Chen, J. Influence of electrolyte composition on microstructure and properties of coatings formed on pure Ti substrate by micro arc oxidation. *Surf. Coat. Technol.* **2018**, *349*, 522–528. [CrossRef]
32. Correa, D.R.N.; Rocha, L.A.; Ribeiro, A.R.; Gemini-Piperni, S.; Archanjo, B.S.; Achete, C.A.; Werckmann, J.; Afonso, C.R.M.; Shimabukuro, M.; Doi, H.; et al. Growth mechanisms of Ca- and P-rich MAO films in Ti-15Zr-*x*Mo alloys for osseointegrative implants. *Surf. Coat. Technol.* **2018**, *344*, 373–382. [CrossRef]
33. Tsai, M.T.; Chang, Y.Y.; Huang, H.L.; Wu, Y.H.; Shieh, T.M. Micro-arc oxidation treatment enhanced the biological performance of human osteosarcoma cell line and human skin fibroblasts cultured on titanium–zirconium films. *Surf. Coat. Technol.* **2016**, *303*, 268–276. [CrossRef]
34. Wang, Y.; Wang, L.; Zheng, H.; Du, C.; Ning, C.; Shi, Z.; Xu, C. Effect of frequency on the structure and cell response of Ca-and P-containing MAO films. *Appl. Surf. Sci.* **2010**, *256*, 2018–2024. [CrossRef]
35. Huang, Q.; Li, X.; Elkhooly, T.A.; Liu, X.; Zhang, R.; Wu, H.; Feng, Q.L.; Liu, Y. The Cu-containing TiO_2 coatings with modulatory effects on macrophage polarization and bactericidal capacity prepared by micro-arc oxidation on titanium substrates. *Colloids Surf. B Biointerfaces* **2018**, *170*, 242–250. [CrossRef]
36. Wang, C.H.; Ma, F.C.; Liu, P.; Chen, J.; Liu, X.K.; Zhang, K.; Li, W.; Han, Q.Y. The influence of alloy elements in Ti6Al4V and Ti35Nb2Ta3Zr on the structure, morphology and properties of MAO coatings. *Vacuum* **2018**, *157*, 229–236. [CrossRef]
37. Hu, H.J.; Qiao, Y.Q.; Meng, F.H.; Liu, X.Y.; Ding, C.X. Enhanced apatite-forming ability and cytocompatibility of porous and nanostructured TiO_2/$CaSiO_3$ coating on titanium. *Colloids Surf. B Biointerfaces* **2013**, *101*, 83–90. [CrossRef]
38. Zhang, R.R.; Liu, X.J.; Xiong, Z.Y.; Huang, Q.L.; Yang, X.; Yan, H. Novel micro/nanostructured TiO_2/ZnO coating with antibacterial capacity and cytocompatibility. *Ceram. Int.* **2018**, *44*, 9711–9719. [CrossRef]
39. Najeeb, S.; Zafar, M.S.; Khurshid, Z.; Zohaib, S.; Hasan, S.M.; Khan, R.S. Bisphosphonate releasing dental implant surface coatings and osseointegration: A systematic review. *J. Taibah Univ. Med Sci.* **2017**, *12*, 369–375. [CrossRef]
40. Daroonparvar, M.; Yajid, M.A.M.; Yusof, N.M.; Bakhsheshi-Rad, H.R.; Hamzah, E. Deposition of duplex MAO layer/nanostructured titanium dioxide composite coatings on Mg–1%Ca alloy using a combined technique of air plasma spraying and micro arc oxidation. *J. Alloy. Compd.* **2015**, *649*, 591–605. [CrossRef]
41. Heimann, R.B. Thermal spraying of biomaterials. *Surf. Coat. Technol.* **2006**, *201*, 2012–2019. [CrossRef]
42. Lima, R.S.; Marple, B.R. Thermal spray coatings engineered from nano-structured ceramic agglomerated powders for structural, thermal barrier and biomedical applications: A review. *Therm. Spray Technol.* **2007**, *16*, 40–63. [CrossRef]
43. Zhou, L.; Zhou, W.C.; Su, J.B. Effect of composition and annealing on the dielectric properties of ZnO/mullite composite coating. *Ceram. Int.* **2012**, *38*, 1077–1083. [CrossRef]
44. Balani, K.; Anderson, R.; Laha, T. Plasma-sprayed carbon nanotube reinforced hydroxyapatite coatings and their interaction with human osteoblasts in vitro. *Biomaterials* **2007**, *28*, 618–624. [CrossRef]

45. Shamray, V.; Sirotinkin, V.; Smirnov, I.; Kalita, V.; Fedotov, A.; Barinov, S.; Komlev, V.; Fedotov, A.; Komlev, V. Structure of the hydroxyapatite plasma-sprayed coatings deposited on pre-heated titanium substrates. *Ceram. Int.* **2017**, *43*, 9105–9109. [CrossRef]
46. Sathish, S.; Geetha, M.; Aruna, S.; Balaji, N.; Rajam, K.; Asokamani, R. Studies on plasma sprayed bi-layered ceramic coating on bio-medical Ti–13Nb–13Zr alloy. *Ceram. Int.* **2011**, *37*, 1333–1339. [CrossRef]
47. Sathish, S.; Geetha, M.; Aruna, S.; Balaji, N.; Rajam, K.; Asokamani, R. Sliding wear behavior of plasma sprayed nanoceramic coatings for biomedical applications. *Wear* **2011**, *271*, 934–941. [CrossRef]
48. Kumari, R.; Majumdar, J.D. Wear Behavior of plasma spray deposited and post heat-treated hydroxyapatite (HA)-based composite coating on titanium alloy (Ti-6Al-4V) substrate. *Metall. Mater. Trans. A* **2018**, *49*, 3122–3132. [CrossRef]
49. Hung, K.Y.; Lo, S.C.; Shih, C.S.; Yang, Y.C.; Feng, H.P.; Lin, Y.C. Titanium surface modified by hydroxyapatite coating for dental implants. *Surf. Coat. Technol.* **2013**, *231*, 337–345. [CrossRef]
50. Yang, Y.C.; Yang, C.Y. Mechanical and histological evaluation of a plasma sprayed hydroxyapatite coating on a titanium bond coat. *Ceram. Int.* **2013**, *39*, 6509–6516. [CrossRef]
51. Rahman, Z.U.; Shabib, I.; Haider, W. Surface characterization and cytotoxicity analysis of plasma sprayed coatings on titanium alloys. *Mater. Sci. Eng. C* **2016**, *67*, 675–683. [CrossRef]
52. Ebrahimi, N.; Hossein, Z.A.S.A.; Vaezi, M.R. A new double-layer hydroxyapatite/alumina-silica coated titanium implants using plasma spray technique. *Surf. Coat. Technol.* **2018**, *352*, 474–482. [CrossRef]
53. Cao, L.; Ullah, I.; Li, N.; Niu, S.; Sun, R. Plasma spray of biofunctional (Mg, Sr)-substituted hydroxyapatite coatings for titanium alloy implants. *J. Mater. Sci. Technol.* **2018**, *35*, 719–726. [CrossRef]
54. Walsh, W.R.; Bertollo, N.; Christou, C.; Schaffner, D.; Mobbs, R.J. Plasma-sprayed titanium coating to polyetheretherketone improves the bone-implant interface. *Spine J.* **2015**, *15*, 1041–1049. [CrossRef]
55. Hickey, D.J.; Lorman, B.; Fedder, I.L. Improved response of osteoprogenitor cells to titanium plasma-sprayed PEEK surfaces. *Colloids Surf. B Biointerfaces* **2019**, *175*, 509–516. [CrossRef]
56. Ke, D.; Vu, A.A.; Bandyopadhyay, A.; Bose, S. Compositionally graded doped hydroxyapatite coating on titanium using laser and plasma spray deposition for bone implants. *Acta Biomater.* **2019**, *84*, 414–423. [CrossRef] [PubMed]
57. Lin, Z.; Li, S.J.; Sun, F.; Ba, D.C.; Li, X.C. Surface characteristics of a dental implant modified by low energy oxygen ion implantation. *Surf. Coat. Technol.* **2019**, *365*, 208–213. [CrossRef]
58. Feng, H.; Yu, Z.; Chu, P.K. Ion implantation of organisms. *Mater. Sci. Eng. R* **2006**, *54*, 49–120. [CrossRef]
59. Fang, J.; Sun, Y.; Ma, H.Y.; Yu, X.L.; Ma, Y.; Ni, Y.X.; Zheng, L.; Zhou, Y.M. Biocompatibility and antibacterial properties of zinc-ion implantation on titanium. *J. Hard Tissue Biol.* **2014**, *23*, 35–43. [CrossRef]
60. Rautray, T.R.; Narayanan, R.; Kim, K.H. Ion implantation of titanium based biomaterials. *Prog. Mater. Sci.* **2011**, *56*, 1137–1177. [CrossRef]
61. Ming, M.; Wan, R.X.; Gong, H.H.; Lv, X.F.; Chu, S.S.; Li, D.J.; Gu, H.Q.; Cheng, P. Study on the in vitro and in vivo antibacterial activity and biocompatibility of novel TiN/Ag multilayers immobilized onto biomedical titanium. *J. Nanosci. Nanotechnol.* **2019**, *19*, 3777–3791.
62. Zhu, C.; Bao, N.R.; Chen, S.; Zhao, J.N. Antimicrobial design of titanium surface that kill sessile bacteria but support stem cells adhesion. *Appl. Surf. Sci.* **2016**, *389*, 7–16. [CrossRef]
63. Li, Y.; Zhao, T.T.; Wei, S.B.; Xiang, Y.; Chen, H. Effect of Ta_2O_5/TiO_2 thin film on mechanical properties, corrosion and cell behavior of the NiTi alloy implanted with tantalum. *Mater. Sci. Eng. C* **2010**, *30*, 1227–1235. [CrossRef]
64. Xu, J.; Ding, G.; Li, J.L.; Yang, S.H.; Fang, B.S.; Sun, H.C.; Zhou, Y.M. Zinc-ion implanted and deposited titanium surfaces reduce adhesion of Streptococccus mutans. *Appl. Surf. Sci.* **2010**, *256*, 7540–7544. [CrossRef]
65. Jin, G.D.; Cao, H.L.; Qiao, Y.Q.; Meng, F.H.; Zhu, H.Q.; Liu, X.Y. Osteogenic activity and antibacterial effect of zinc ion implanted titanium. *Colloids Surf. B Biointerfaces* **2014**, *117*, 158–165. [CrossRef]
66. Shanaghi, A.; Chu, P.K. Enhancement of mechanical properties and corrosion resistance of NiTi alloy by carbon plasma immersion ion implantation. *Surf. Coat. Technol.* **2018**, *365*, 52–57. [CrossRef]
67. Vlcak, P.; Fojt, J.; Weiss, Z.; Kopeček, J.; Perina, V. The effect of nitrogen saturation on the corrosion behaviour of Ti-35Nb-7Zr-5Ta beta titanium alloy nitrided by ion implantation. *Surf. Coat. Technol.* **2019**, *358*, 144–152. [CrossRef]
68. Chouirfa, H.; Bouloussa, H.; Migonney, V.; Falentin-Daudré, C. Review of titanium surface modification techniques and coatings for antibacterial applications. *Acta Biomater.* **2019**, *83*, 37–54. [CrossRef]

69. Kim, S.; Park, C.; Cheon, K.H.; Jung, H.D.; Song, J.; Kim, H.E.; Jang, T.S. Antibacterial and bioactive properties of stabilized silver on titanium with a nanostructured surface for dental applications. *Appl. Surf. Sci.* **2018**, *451*, 232–240. [CrossRef]
70. Weng, F.; Chen, C.Z.; Yu, H.J. Research status of laser cladding on titanium and its alloys: A review. *Mater. Des.* **2014**, *58*, 412–425. [CrossRef]
71. Kurella, N.B.; Dahotre, A. Review paper: Surface modification for bioimplants: The role of laser surface engineering. *J. Biomater. Appl.* **2005**, *20*, 5–50. [CrossRef]
72. Du Plooy, R.; Akinlabi, E.T. Analysis of laser cladding of titanium alloy. *Mater. Today Proc.* **2018**, *5*, 19594–19603. [CrossRef]
73. Long, J.; Fan, P.; Gong, D.; Jiang, D.; Zhang, H.; Li, L.; Zhong, M. Super-hydrophobic surfaces fabricated by femtosecond laser with tunable water adhesion: From lotus leaf to rose petal. *ACS Appl. Mater. Interfaces* **2015**, *7*, 9858–9865. [CrossRef]
74. Tian, Y.; Chen, C.; Li, S. Research progress on laser surface modification of titanium alloys. *Appl. Surf. Sci.* **2005**, *242*, 177–184. [CrossRef]
75. Antalya, H.S.L.; Bolander, J.; Rustom, L.E.; Johnson, A.W.; Luyten, F.P.; Picart, C. Bone regeneration strategies: Engineered scaffolds, bioactive molecules and stem cells current stage and future perspectives. *Biomaterials* **2018**, *180*, 143–162.
76. Das, R.K.; Zouani, O.F. A review of the effects of the cell environment physicochemical nanoarchitecture on stem cell commitment. *Biomaterials* **2014**, *35*, 5278–5293. [CrossRef]
77. Shinonaga, T.; Tsukamoto, M.; Kawa, T. Formation of periodic nanostructures using a femtosecond laser to control cell spreading on titanium. *Appl. Phys. B.* **2015**, *119*, 493–496. [CrossRef]
78. Cunha, A.; Zouani, O.F.; Plawinski, L. Human mesenchymal stem cell behavior on femtosecond laser-textured Ti-6Al-4V surfaces. *Nanomedicine* **2015**, *10*, 725–739. [CrossRef] [PubMed]
79. Lee, B.E.J.; Exir, H.; Weck, A. Characterization and evaluation of femtosecond laser-induced sub-micron periodic structures generated on titanium to improve osseointegration of implants. *Appl. Surf. Sci.* **2018**, *441*, 1034–1042. [CrossRef]
80. Marticorena, M.; Corti, G.; Olmedo, D. Laser surface modification of Ti implants to improve osseointegration. *J. Appl. Phys.* **2007**, *59*, 662–665. [CrossRef]
81. Trtica, M.; Stasic, J.; Batani, D.; Benocci, R.; Narayanan, V.; Ciganovic, J. Laser-assisted surface modification of Ti-implant in air and water environment. *Appl. Surf. Sci.* **2018**, *428*, 669–675. [CrossRef]
82. Hsiao, W.T.; Chang, H.C.; Nanci, A.; Durand, R. Surface microtexturing of Ti–6Al–4V using an ultraviolet laser system. *Mater. Des.* **2016**, *90*, 891–895. [CrossRef]
83. Kumari, R.; Scharnweber, T.; Pfleging, W.; Besser, H.; Majumdar, J.D. Laser surface textured titanium alloy (Ti–6Al–4V)–Part II–Studies on bio-compatibility. *Appl. Surf. Sci.* **2015**, *357*, 750–758. [CrossRef]
84. Paital, S.R.; Balani, K.; Agarwal, A.; Dahotre, N.B. Fabrication and evaluation of a pulse laser-induced Ca–P coating on a Ti alloy for bioapplication. *Biomed. Mater.* **2009**, *4*, 015009. [CrossRef]
85. Kurella, A.; Dahotre, N.B. Laser induced hierarchical calcium phosphate structures. *Acta Biomater.* **2006**, *2*, 677–683. [CrossRef]
86. Bose, S.; Robertson, S.F.; Bandyopadhyay, A. Surface modification of biomaterials and biomedical devices using additive manufacturing. *Acta Biomater.* **2018**, *66*, 6–22. [CrossRef] [PubMed]
87. Koch, C.; Johnson, S.; Kumar, D.; Jelinek, M.; Chrisey, D.; Doraiswamy, A. Pulsed laser deposition of hydroxyapatite thin films. *Mater. Sci. Eng. C* **2007**, *27*, 484–494. [CrossRef]
88. Paital, S.R.; He, W.; Dahotre, N.B. Laser pulse dependent micro textured calcium phosphate coatings for improved wettability and cell compatibility. *J. Mater. Sci. Mater. Med.* **2010**, *21*, 2187–2200. [CrossRef]
89. Zheng, M.; Fan, D.; Li, X.K. Microstructure and in vitro bioactivity of laser-cladded bioceramic coating on titanium alloy in a simulated body fluid. *J. Alloy. Compd.* **2010**, *489*, 211–214. [CrossRef]
90. Ranjan, B.R.; Abshar, H.; Ravi, S.M. Laser cladding with HA and functionally graded TiO_2-HA precursors on Ti–6Al–4V alloy for enhancing bioactivity and cyto-compatibility. *Surf. Coat. Technol.* **2018**, *352*, 420–436.
91. Bandyopadhyay, A.; Bose, S.; Roy, M. MgO-doped tantalum coating on Ti: Microstructural study and biocompatibility evaluation. *ACS Appl. Mater. Interfaces* **2012**, *4*, 577–580.
92. Deng, B.W.; Bruzzaniti, A.; Cheng, G.J. Enhancement of osteoblast activity on nanostructured NiTi/hydroxyapatite coatings on additive manufactured NiTi metal implants by nanosecond pulsed laser sintering. *Int. J. Nanoned.* **2018**, *13*, 8217–8230. [CrossRef]

93. Hseni, E.; Zalnezhad, E.; Bushroa, A.R. Comparative investigation on the adhesion of hydroxyapatite coating on Ti–6Al–4V implant: A review paper. *Int. J. Adhes. Adhes.* **2014**, *48*, 238–257.
94. Miranda, G.; Sousa, F.; Costa, M.; Bartolomeu, F.; Silva, F.; Carvalho, O. Surface design using laser technology for Ti-6Al-4V-hydroxyapatite implants. *Opt. Technol.* **2019**, *109*, 488–495. [CrossRef]
95. Liu, W.C.; Wang, H.Y.; Chen, L.C.; Huang, S.W.; Wu, C.T.; Chung, R.J. Hydroxyapatite/tricalcium silicate composites cement derived from novel two-step sol-gel process with good biocompatibility and applications as bone cement and potential coating materials. *Ceram. Int.* **2019**, *45*, 5668–5679. [CrossRef]
96. Owens, G.; Singh, R.K.; Foroutan, F.; Alqaysi, M. Sol–gel based materials for biomedical applications. *Prog. Mater Sci.* **2016**, *77*, 1–79. [CrossRef]
97. Çomakli, O.; Yazici, M.; Yetim, T.; Yetim, A.F.; Çelik, A. The Effects of aging time on the structural and electrochemical properties of composite coatings on Cp-Ti substrate. *J. Bionic Eng.* **2017**, *14*, 532–539. [CrossRef]
98. Çomaklı, O.; Yazıcı, M.; Kovacı, H.; Yetim, T.; Yetim, A.F.; Çelik, A. Tribological and electrochemical properties of TiO_2 films produced on Cp-Ti by sol-gel and SILAR in bio-simulated environment. *Surf. Coat. Technol.* **2018**, *352*, 513–521. [CrossRef]
99. Balaganapathi, T.; Kaniamuthan, B.; Vinoth, S.; Thilakan, P. PEG assisted synthesis of porous TiO_2 using sol-gel processing and its characterization studies. *Mater. Chem. Phys.* **2017**, *189*, 50–55. [CrossRef]
100. Catauro, M.; Bollino, F.; Veronesi, P.; Lamanna, G. Influence of PCL on mechanical properties and bioactivity of ZrO_2-based hybrid coatings synthesized by sol–gel dip coating technique. *Mater. Sci. Eng. C* **2014**, *39*, 344–351. [CrossRef]
101. Anjaneyulu, U.; Priyadarshini, B.; Stango, S.A.X.; Chellappa, M.; Geetha, M.; Vijayalakshmi, U. Preparation and characterisation of sol–gel-derived hydroxyapatite nanoparticles and its coatings on medical grade Ti-6Al-4V alloy for biomedical applications. *Mater. Technol.* **2017**, *32*, 800–814. [CrossRef]
102. Greer, A.I.; Lim, T.S.; Brydone, A.S.; Gadegaard, N. Mechanical compatibility of sol–gel annealing with titanium for orthopaedic prostheses. *Mater. Sci. Mater. Med.* **2016**, *27*, 21–27. [CrossRef]
103. Ergün, Y.; Başpınar, M.S. Effect of acid passivation and H_2 sputtering pretreatments on the adhesive strength of sol-gel derived Hydroxyapatite coating on titanium surface. *Int. J. Hydrogen Energy.* **2017**, *42*, 20420–20429. [CrossRef]
104. Roest, R.; Latella, B.; Heness, G.; Ben-Nissan, B. Adhesion of sol–gel derived hydroxyapatite nanocoatings on anodised pure titanium and titanium (Ti6Al4V) alloy substrates. *Surf. Coat. Technol.* **2011**, *205*, 3520–3529. [CrossRef]
105. Yang, S.; Zhou, F.; Xiao, T.; Xu, D.B.; Li, Z.; Xiao, Z.; Xiao, Z.A. Surface modification with SiO_2 coating on biomedical TiNi shape memory alloy by sol−gel method. *Trans. Nonferrous Met. Soc.* **2015**, *25*, 3723–3728. [CrossRef]
106. Andrea Alcantara-Garcia, A.; Garcia-Casas, A.; Jimenez-Morales, A. Electrochemical study of the synergic effect of phosphorus and cerium additions on a sol-gel coating for Titanium manufactured by powder metallurgy. *Prog. Org. Coat.* **2018**, *124*, 267–274. [CrossRef]
107. Catauro, M.; Bollino, F.; Papale, F. Surface modifications of titanium implants by coating with bioactive and biocompatible poly (ε-caprolactone)/SiO_2 hybrids synthesized via sol–gel. *Asian J. Chem.* **2018**, *11*, 1126–1133. [CrossRef]
108. Sharma, V.; Prakash, U.; Kumar, B.V.M. Surface composites by friction stir processing: A review. *J. Mater. Process. Technol.* **2015**, *224*, 117–134. [CrossRef]
109. Misra, R.; Thein-Han, W.; Pesacreta, T.; Hasenstein, K.; Somani, M.; Karjalainen, L. Cellular response of preosteoblasts to nanograined/ultrafine-grained structures. *Acta Biomater.* **2009**, *5*, 1455–1467. [CrossRef] [PubMed]
110. McNelley, T.R. Friction stir processing (FSP): Refining microstructures and improving properties. *Rev. Met.* **2010**, *46*, 149–156. [CrossRef]
111. Węglowski, M.S. Friction stir processing–State of the art. *Arch. Civ. Mech. Eng.* **2018**, *18*, 114–129. [CrossRef]
112. Khodabakhshi, F.; Gerlich, A. Potentials and strategies of solid-state additive friction-stir manufacturing technology: A critical review. *J. Manuf. Process.* **2018**, *36*, 77–92. [CrossRef]
113. Li, B.; Shen, Y.; Hu, W.; Luo, L. Surface modification of Ti–6Al–4V alloy via friction-stir processing: Microstructure evolution and dry sliding wear performance. *Surf. Coat. Technol.* **2014**, *239*, 160–170. [CrossRef]

114. Wang, L.Q.; Xie, L.E.; Liu, Y.T.; Zhang, L.C.; Chen, L.Y.; Meng, Q.; Qu, J.; Zhang, D.; Lu, W.J. Microstructure evolution and superelastic behavior in Ti-35Nb-2Ta-3Zr alloy processed by friction stir processing. *Acta Mater.* **2017**, *131*, 499–510. [CrossRef]
115. Gu, H.; Ding, Z.H.; Yang, Z.; Yu, W.Q.; Wang, L.Q. Microstructure evolution and electrochemical properties of TiO_2/Ti-35Nb-2Ta-3Zr micro/nano-composites fabricated by friction stir processing. *Mater. Des.* **2019**, *169*, 10768. [CrossRef]
116. Xie, L.C.; Wang, L.Q.; Wang, K.S.; Yin, G.L.; Fu, Y.F. TEM characterization on microstructure of Ti–6Al–4V/Ag nanocomposite formed by friction stir processing. *Materialia* **2018**, *3*, 139–144. [CrossRef]
117. Zhu, C.; Lv, Y.; Qian, C. Proliferation and osteogenic differentiation of rat BMSCs on a novel Ti/SiC metal matrix nanocomposite modified by friction stir processing. *Sci. Rep.* **2016**, *6*, 38875. [CrossRef] [PubMed]
118. Qin, D.Q.; Shen, H.R.; Shen, Z.K.; Chen, H.Y.; Li, F. Manufacture of biodegradable magnesium alloy by high speed friction stir processing. *J. Manuf. Process.* **2018**, *36*, 22–32. [CrossRef]
119. Lv, Y.T.; Ding, Z.H.; Xue, J.; Sha, G.; Wang, L.Q. Deformation mechanisms in surface nano-crystallization of low elastic modulus Ti-6Al-4V/Zn composite during severe plastic deformation. *Scr. Mater.* **2018**, *157*, 142–147. [CrossRef]
120. Rahmati, R.; Khodabakhshi, F. Microstructural evolution and mechanical properties of a friction-stir processed Ti-hydroxyapatite (HA) nanocomposite. *J. Mech. Behav. Biomed. Mater.* **2018**, *88*, 127–139. [CrossRef]
121. Zhang, C.J.; Ding, Z.H.; Xie, L.H.; Zhang, L.C.; Wu, L.Z.; Fu, Y.F.; Wang, L.Q.; Lu, W.J. Electrochemical and in vitro behavior of the nanosized composites of Ti-6Al-4V and TiO_2 fabricated by friction stir process. *Appl. Surf. Sci.* **2017**, *423*, 331–339. [CrossRef]
122. Yang, Z.; Gu, H.; Sha, G.; Lu, W.J.; Yu, W.Q.; Zhang, W.J.; Fu, Y.J.; Wang, K.S.; Wang, L.Q. TC4/Ag metal matrix nanocomposites modified by friction stir processing: Surface characterization, antibacterial property, and cytotoxicity in vitro. *ACS Appl. Mater. Interfaces* **2018**, *10*, 41155–41166. [CrossRef]
123. Wang, L.Q.; Qu, J.; Chen, L.Y.; Meng, Q.; Zhang, L.C.; Qin, J.N. Investigation of deformation mechanisms in beta-type Ti-35Nb-2Ta-3Zr alloy via FSP leading to surface strengthening. *Metall. Mater. Trans. A* **2015**, *46A*, 4813–4818. [CrossRef]
124. Ding, Z.H.; Zhang, C.J.; Xie, L.C.; Zhang, L.C.; Wang, L.Q.; Lu, W.J. Effects of friction stir processing on the phase transformation and microstructure of TiO_2-compounded Ti-6Al-4V alloy. *Metall. Mater. Trans. A* **2016**, *47A*, 5675–5679. [CrossRef]