Calcium Phosphate Coatings for Metallic Orthopedic Biomaterials

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1 Introduction

Metallic implant materials are widely used for clinical applications because of a combination of superior mechanical properties and good durability when compared to ceramic and polymeric materials. However, they still did not achieve satisfactory functionalities for specific biomedical applications, such as osteointegration in bone implants, controllable degradation rate for biodegradable implants, and antibacterial functions for the desired clinical applications. When the metallic material is implanted into the living tissue, the surface properties of the implant material play extremely important role in the interactions between the biological environment and the artificial implant [1, 2]. Therefore, surface functionalizations are of particular interest and are a requirement to improve surface bioactivity and other biofunctionalities for biomedical applications.

Calcium phosphate (CaP) is the main mineral phase of bone tissues in vertebrates, and thus has a great intrinsic advantage as a bone substitute for bone reconstructive

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Table 1 Summary of main functions of CaP coatings emphasized in this chapter

Main functions	Examples	Reference
Biocompatibility—osteointegration	Bone-like carbonated apatitic (BCA) biomimetic coating on dense Ti6Al4V alloys and porous Ta cylinders	[8]
	CaP-based composite coatings with biomolecules (collagen, bone morphogenetic protein-2, etc.)	[4, 9, 10]
Corrosion resistance	DCPD, HA, and FHA coatings on biodegradable Mg alloys	[11]
Antibacterial property	CaP-based composite coatings with antimicrobial biomolecules (AMP)	[12]
	CaP coatings doped with Ag, Cu, Zn, and F	[13–17]

surgery. The intrinsic biocompatibility of CaPs can ensure that they would not be recognized as foreign materials in the body and is also known to support osteoblast adhesion and proliferation [3]. However, the low fatigue brittleness of the CaP bulk material limits its development as a load-bearing implant material [115]. Thus, CaPs are preferred to be used as a cement and as a coating material for biomedical applications [5–7]. CaP coatings were developed onto the surface of metallic implants to combine the mechanical strength of metals with the excellent biological functions of CaP ceramics. The highlighting studies on CaPs emphasized in this chapter are summarized in Table 1.

2 Metals for Biomedical Implant Applications

Metals have been exploited for biomedical application since an iron dental implant was first recorded to be integrated into bone to repair the human body around 200 A.D [18, 19]. Compared to polymers and ceramics, metals can provide a combination of required properties for biomedical applications, including the appropriate physical and mechanical properties, and good corrosion and wear resistance. They account for 70% of implants including for orthopedics: knee joints, total hip joints, bone plates, fracture fixation wires, pins, screws, and plates; and for cardiovascular: artificial heart valves, vascular stents, and pacemaker leads [20].

Although pure metals are widely used, alloys provide improved strength and corrosion resistance. Up to now, the three most used metals for implants are stainless steels (SS), cobalt-chromium (Co–Cr) alloys and titanium (Ti) alloys [20]. SS316L is one of the most widely known SS, and has been highly recommended and applied clinically for quite a long time [21] because of its adequate physical and mechanical properties and superior corrosion resistance. To limit the Ni content in SS, a high-nitrogen SS was introduced and has been proven to possess improved biocompatibility combined with excellent corrosion and wear resistance [22]. Co–Cr alloys, mainly represented as Co–Cr–Mo and Co–Cr–W–Ni series, are characterized by their high corrosion and wear resistance [23]. They have been established as metal-
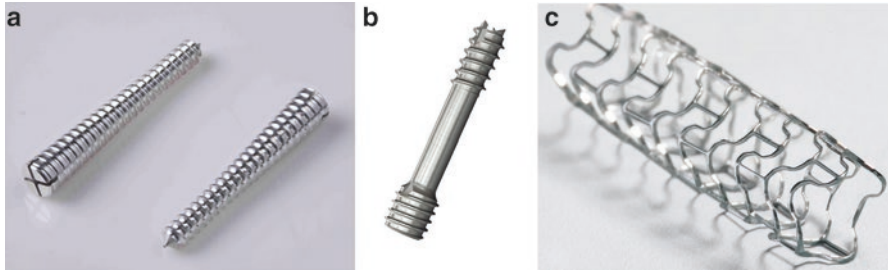
Fig. 1 Examples of implants made of biodegradable metals: (**a**) magnesium absorbable stent, (**b**) magnesium compression bone screw, and (**c**) magnesium headless bone screw [28]

lic implants such as artificial joints, denture wires, and stents [24]. Pure Ti and Ti–6Al–4V alloy have been previously used as biomaterials for constructing implant devices [25]. A number of β-type Ti alloys with nontoxic and allergy-free elements and low Young's modulus have been developed to avoid the harmful elements in Ti–6Al–4V and the stress shielding effect.

Biodegradable metals are defined as "metals expected to corrode gradually in vivo, with an appropriate host response elicited by released corrosion products, then dissolve completely upon fulfilling the mission to assist with tissue healing with no implant residues" [26]. Compared with the conventional inert implant metals as mentioned above, the degradation property of biodegradable metals as temporary implants can help to avoid subsequent removal surgery, thereby accelerating the entire healing process with a simultaneous reduction in health risks, costs and scarring [5, 27].

Recently, there are at least three companies that have launched commercial biodegradable metal products or prototypes as shown in Fig. 1 [28]. Up to now, magnesium (Mg), iron (Fe) and zinc (Zn) are the three biodegradable metals that have been proposed for temporary implants in their pure states or as the matrix for making alloys and composites [18], while orthopedic, cardiovascular and pediatric implants are three targeted applications [27]. The most recent development of these three metals is described in the following paragraphs. A more detailed discussion can be found in a recent review by Zheng et al. [26].

3 Surface Properties of the Implant Material

When a metallic material is implanted into the living tissue, an interface is created between the implant material and the surrounding tissues. It is of significance to ensure that the implants with specific surface features be recognized by the highly precocious ability of biological systems at the implant–tissue interface [1, 2]. The implant surfaces with different morphology, chemistry, and wettability will strongly influence the material-cell interaction and thereby tissue integration at the interface.
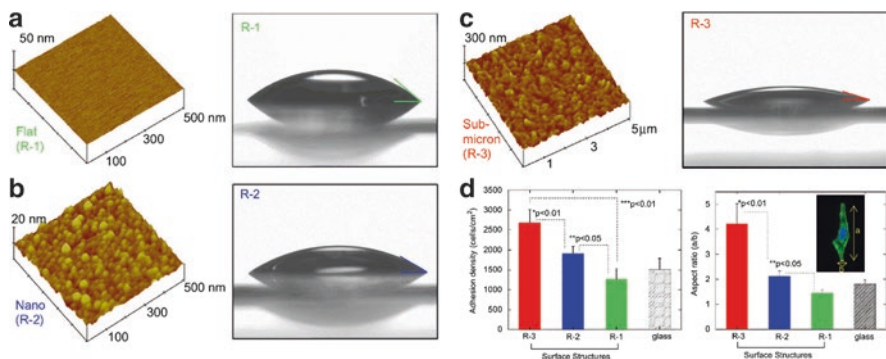
Fig. 2 Contact angles showed increased hydrophilicity on (**a**) flat, (**b**) nanometer and (**c**) sub-micron surface-featured titanium. (**d**) Adhesion density showed that sub-micron structures led to the best adhesion density (seeding density was 3500 cells/cm²), and cell aspect ratios showed oriented cell morphology for flat, nanometer and sub-micron structures (increased right to left). Note that cell aspect ratios were calculated by the length of a single cell divided by its width (inset image of (**d**)). All error bars are mean ± SEM; n = 3; *p < 0.01 (compared to R-2) and **p < 0.05 (compared to R-1) [30]

Surface morphology: The morphological features such as surface roughness [25, 29] and its topography [30, 31] can strongly influence the protein adsorption [25], cell adhesion [30], cell migration and differentiation [32, 33]. Generally, surface roughness can affect cell behavior directly via enhanced formation of focal contacts or indirectly through selective adsorption of serum proteins required for cell attachment [29], while substratum topography with different scales (*e.g.* micro-, sub-micro- and nanometer scale [30, 33, 34], as shown in Fig. 2) and features (*e.g.* randomly or evenly distributed pores, grooves, nodes, ridges, and pillars [34–36]) have direct effects on the abilities of cells to produce organized cytoskeletal arrangements [34]. It should be mentioned that cellular responses to substratum topography may be very different for different cell types. For example, most cell types were observed to exhibit alignment to grooves, but some were not aligned [34, 37].

Surface chemistry: The surface chemistry of an implanted material is important and can be altered to induce cell adhesion and spreading [38–40]. It has been demonstrated by substantial research efforts that surface functional groups can affect protein adsorption and subsequent cellular responses [41–43]. In general, hydrophilic functionality provides low interfacial free energy resulting in reduced protein adsorption, cell adhesion, and blood compatibility [44, 45]. As for metallic implant materials, different chemical compositions of different phases and grain boundaries may also have different interactions with cells [46].

Surface wettability: Surface wettability of the implant material is an important criterion to control protein adsorption followed by cell attachment because the wetting of the implant material by physiological fluids is the first and the foremost event during implantation [47]. It is well established that proteins tend to bind to hydrophobic surfaces, and cells typically adhere selectively on the hydrophilic regions, although the cell behavior is also dependent on the cell type and material used
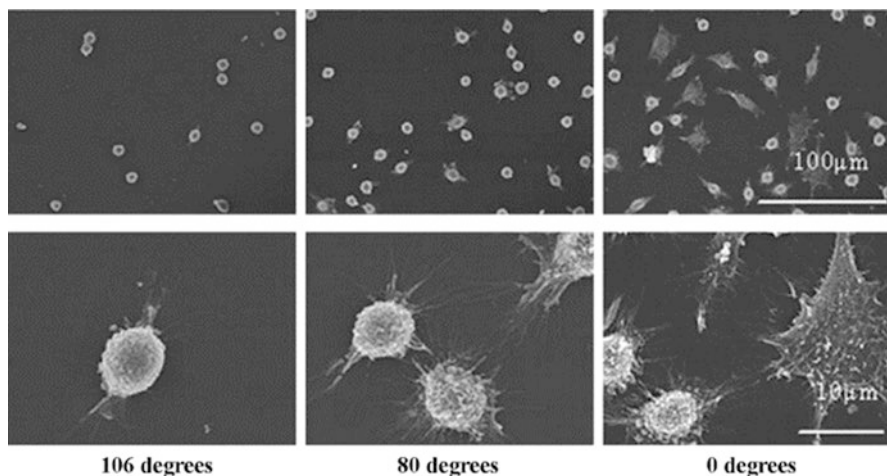
Fig. 3 SEM of L929 attached to surfaces with different wettability in 24 h at low magnification (top, original: 500×) and high magnification (bottom, original: 3000×) [56]

[48–50]. Generally, few cells can adhere to superhydrophobic surfaces, and cells typically showed a round morphology upon attachment [51]. However, surface chemistry and topography are the two most important factors that affect the surface wettability, i.e., surface wettability can be preferentially tuned from hydrophobic to hydrophilic through independently controlling surface chemistry and topography [52–55], so it is difficult to discuss the effect of wettability without considering these two factors. For example, L929 cell attachment was studied on surfaces with varying surface wettability of hexamethyldisiloxane modified by plasma polymerization followed by O_2 plasma treatment [56], as shown in Fig. 3. It can be observed that the hydrophilic surface has more cells attached as compared to the hydrophobic surface after 24 h of incubation, but the decrease in contact angle resulted from the introduction of more hydrophilic—COOH groups and the decrease of hydrophobic groups, such as –CH_3, on the surface [56].

4   Calcium Phosphate Coatings on Biomedical Metals

As mentioned above, metallic biomaterials are exploited mainly due to their outstanding mechanical properties, but they do not possess functionalities for specific biomedical applications, such as osteointegration in bone implants, controllable degradation rate for biodegradable implants, and antibacterial functions for the desired clinical applications. Because the surface properties of the implant material play extremely important roles in the interactions between the biological environment and the artificial implant material [1, 2], it has been proved that the biomedical performance of these metallic biomaterials can be significantly influenced by

surface treatments, such as polishing, oxidation, passivation, coating modification, ion implantation, etc. [38, 57]. Compared with other routines, surface modification with biocompatible and biofunctional coatings can not only improve the surface biocompatibility for the controlled implant/tissue interfacial response, but also supply the controllable degradation rate and various biofunctions [7, 58].

Because bone tissue is a natural composite of inorganic CaP-based ceramics and organic proteins [59], CaPs have a great advantage that they would not be recognized as foreign materials in the body and thus have intrinsic biocompatibility. In addition, CaPs are also known to support osteoblast adhesion and proliferation [3]. Therefore, CaPs have numerous featured clinical orthopedic applications, such as total and partial hip components, cement for defect bone fillings, and coating materials on metallic implants. Based on the chemical composition, synthetic CaPs for biomedical applications are mainly hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$), alpha- or beta-tricalcium phosphate (α- or β-TCP, $Ca_3(PO_4)_2$), biphasic calcium phosphates (BCPs) for mixtures of HA and β-TCP, dicalcium phosphate dihydrate (DCPD, $CaHPO_4·2H_2O$), anhydrous calcium phosphate (ADCP, $CaHPO_4$), and octacalcium phosphate (OCP, $Ca_8(HPO_4)_2(PO_4)_4·5H_2O$). The biomedical performance of CaP ceramics is closely related to their solubility. CaP ceramics have different solubility, and the comparative extent of dissolution is: DCPD > ADCP > OCP > α-TCP > β-TCP > HA [5]. The dissolution of BCPs depends on the β-TCP/HA ratio; the higher the ratio, the higher the extent of dissolution [60], which is also the general trend for different CaP ceramics [5].

CaP coatings were developed onto the surface of metallic implants to combine the mechanical strength of metals with the excellent biological properties of CaP ceramics. Many methods have been developed to deposit CaP coatings on metal implants: plasma-spraying, biomimetic precipitation, sputtering, sol–gel, electrophoretic and electrochemical deposition, and ion beam dynamic mixing deposition [5–7, 47]. In the following sections, various functions, including biocompatibility—osteointegration, corrosion resistance, and antibacterial properties, of CaP coatings on biomedical metals are discussed.

4.1 Biocompatibility: Osteointegration

Biocompatibility is the ability of the materials to perform in the presence of an appropriate host for a specific application [61], which is required for all biomedical materials, including metallic implant materials. In early studies, biocompatibility was simply equated to biologically inactivity and chemically inertness, and thus no harmful effect on the human tissues. However, with recent developments in biotechnology, biological activity is required for particular applications, such as temporary implants, drug and gene delivery systems.

In the case of bone implants, it is generally accepted that osteoprogenitor cells migrate to the implant site and differentiate into osteoblasts that make bone. The requirement for biocompatibility is that the material should integrate with the bone,

i.e., osteointegration [62]. SS and Ti alloys have been commonly used in the clinics for fracture fixation, and new bone formation can be observed on the surface of the fixation devices, especially those made of Ti alloys because of their good biocompatibility. A thin non-mineral layer was generally generated between metallic implants and bones, but there was still no true adhesion observed at the implant/bone interface [63]. In this case, the bond associated with osteointegration is attributed to mechanical interlocking of the metallic surface asperities and pores in the bone [64]. In order to make metallic biomaterials biologically bond to bones, surface functionalization methods have been proposed to improve bone conductivity or bioactivity.

It has been well-recognized that CaP coatings can lead to faster biological fixation and better clinical success rates in the long-term than uncoated implants due to the superior initial rate of osseointegration [8, 65–67]. Among numerous surface modification methods, plasma-spraying is the only method that has been used for Ti dental implants in clinical practice, due to its high deposition rate and the ability to coat large areas [68]. However, plasma-spraying coating has some serious concerns, such as the poor adhesion of the thick coating, phase change during the high-temperature coating process, and particle release and delamination during clinical applications [47, 68–70]. In order to overcome these drawbacks, biomimetic precipitation has drawn more attention when compared to the other methods. Inspired by the natural CaP mineralization process, the precipitation process is conducted in a physiological environment at low temperatures and the deposited coating is biologically identical to bone apatite [8, 69, 71]. For example, a homogeneous bone-like carbonated apatitic (BCA) biomimetic coating was applied onto dense Ti6Al4V alloys and porous Ta cylinders, respectively (Fig. 4a), by immersion into simulated body fluid at 37 °C and then at 50 °C for 24 h [8]. The in vivo implantation test in the femoral diaphysis of adult female goats showed that the bone contact was always significantly higher for the BCA-coated implants than the corresponding non-coated ones (Fig. 4b, c), which indicates that the BCA coating enhances bone integration of these two metallic implants.

As mentioned above, bone can be regarded as composites of the organic matrix strengthened by the inorganic CaP phase (carbonated HA) [59], so the development of organic–inorganic composite coatings inspired by the unique nano-composite structure of bone tissue have become a hot topic for implant surface functionalization. In addition, there are clinical problems related to poor adhesion and thus limited osteoconductivity of current CaP coatings [72], together with uncontrollable loading efficiency or release kinetics of the superficially adsorbed biomolecules [73, 74]. Hence, biomolecule–CaP composite coatings can supply superior properties over the individual components. For example, the ductile properties of collagen can compensate for the poor fracture toughness of CaPs [4], and also promote CaP coating adhesion, cell adhesion and thus fixation of the metallic implant [68, 75]; the osteoconductivity and bone regeneration at the tissue–implant interface can be improved greatly by immobilizing growth factors such as bone morphogenetic protein-2 (BMP-2) and TGF-β to the CaP coating [9, 10]; and a CaP coating can help to delay and sustain growth factor and DNA delivery [76, 77].
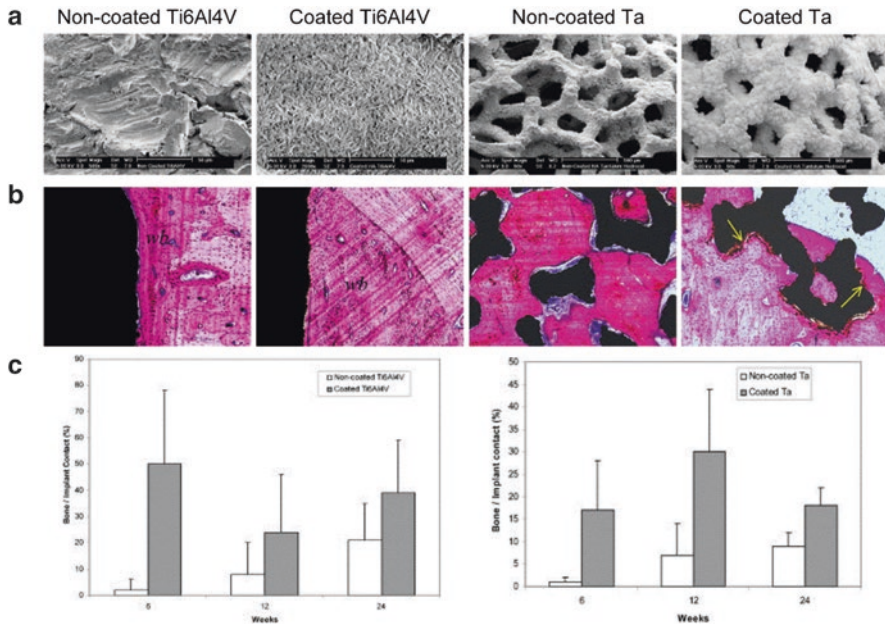
Fig. 4 (**a**) ESEM micrographs of non-coated and BCA-coated Ti6Al4V (grit-blasted) and porous Ta. (**b**) Non-decalcified histological sections of the corresponding dense Ti6Al4V implants (at magnification 40×) and porous Ta implants (at magnification 100×). (**c**) Bone–implant contact at 6, 12, and 24 weeks of implantation for non-coated and BCA-coated Ti6Al4V and porous Ta specimens. All photos have been taken in the cortical bone region and thus at approximately similar locations, that is, the edge of implants. The black zone corresponds to the implant and the purple zone corresponds to bone. *wb* indicates woven or *de novo* bone. Stain: methylene blue and basic fuchsin [8]

4.2 Corrosion Resistance

Corrosion is the degradation of a material's properties due to interactions with the environment [78]. Corrosion deterioration of metals is one of the most important considerations for many applications. Corrosion of metals depend on the metal composition and the corrosive media in the surrounding environment. Metallic implant materials initially contact and react with physiological fluids after implantation in vivo. Nonferrous metals and SS generally have high corrosion resistance due to the presence of a protective passive layer (*e.g.* the titanium oxide film on Ti and chromium oxide layer for SS). However, the high concentration of chloride ions in physiological fluids and the pH changes after implantation can cause and accelerate corrosion in vivo, which produces harmful metal ions to cause toxicity and allergic reactions, and also deteriorates the mechanical properties of the implants [79, 80]. Therefore, good corrosion resistance has been proposed as one of the main selection criteria of biomaterials [81, 82].

In order to inhibit or control corrosion in vivo, a wide variety of approaches has been developed, including surface coatings, alloying elements, surface mechanical treatment, etc. [78]. The application of surface coatings is the most suitable route for metallic implant materials because the designed coating could also act as the biofunctional agent in vivo, in addition to offering effective physical protection. Thus, the CaP coating and composite coatings could also be used to effectively protect metallic implants from corrosion.

Biodegradable metals proposed as temporary implants are special cases for corrosion resistance and should be treated differently for surface modification. Preliminary animal tests showed that the biodegradation rate of Fe alloys is very low [27, 83]. Hence, in order to achieve a faster degradation, research has focused on the development of new kinds of Fe alloys instead of surface modification. There are still some attempts, mainly ion implantation with oxides [84], lanthanum [85], and nitride [86], and the results showed improved surface biocompatibility but slower degradation rate. As for Zn alloys, the degradation rate is basically in line with clinical demand [87, 88], so corrosion rate control is not difficult or even necessary. On the other hand, biodegradability is a double-edged sword for Mg and its alloys because of the extremely high degradation rate of the Mg-alloy implant in body fluids not only deteriorates its mechanical integrity before the tissue has sufficiently healed, but also releases too much hydrogen gas, which results in subcutaneous bubbles [89]. There are several reviews specializing on the corrosion protection of biodegradable Mg and its alloys [58, 90, 91], and the CaP-based coating is one of the hottest topics [5, 6, 69]. In addition to the CaP-based coating methods mentioned above, chemical conversion deposition is a noteworthy method specialized for Mg alloys, because the electrochemical potential heterogeneity between the α-Mg phase and β phase in Mg alloys turns out to be a positive factor during the conversion coating process, although it is the main reason for galvanic coupling during the corrosion process [92–94]. It is a simple and easily controlled method to produce uniform and well-adhered CaP coatings on Mg alloys and composites [94–98], especially for the complex-shaped components of the orthopedic implant. It has been shown previously that CaP coatings can increase corrosion resistance and improve the surface bioactivity of Mg alloys [97–101]. Fig. 5 shows the typical morphologies and the corresponding anti-corrosion performances of several different CaP coating examples [11].

4.3   Antibacterial Property

Another challenge with medical implants is the high risk of microbial growth on implanted devices. Biomaterial-associated infection is one of the most frequent complications of medical implants and devices. Biofilms are composed of structured micro-organisms adherent firmly to the implant surface and will produce extracellular polymeric substances, which makes them resistant to the antibacterial molecules and cells mobilized by the host [102, 103].
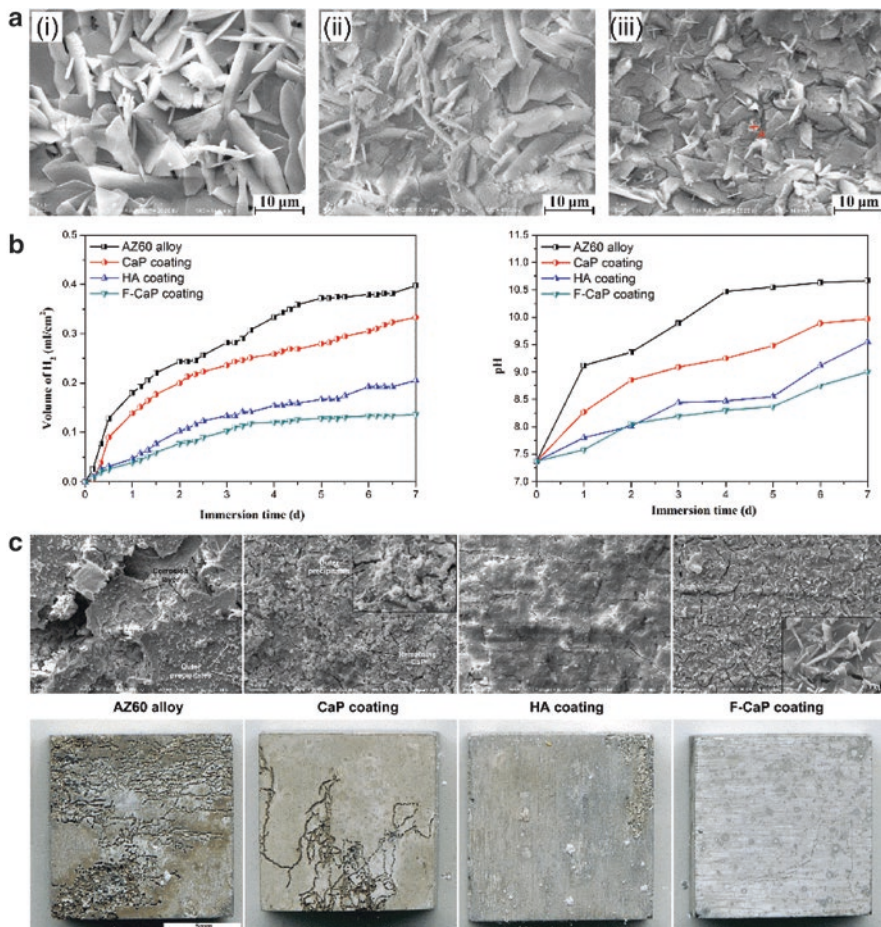
Fig. 5 (**a**) The surface morphologies of (**i**) CaP, (**ii**) HA and (**iii**) fluorine post-treated CaP (F-CaP) coatings. (**b**) Hydrogen volume and pH evolution as a function of immersion time in the immersion test in SBF. (**c**) Mineralization morphologies and the corresponding appearance photographs (after removing corrosion products) of the uncoated and coated samples immersed in SBF for 7 days [11]

In order to develop an antibacterial surface preventing biomedical implant-related infections, the first strategy to be explored was the local delivery of biocides, with the development of bactericidal coatings that release antimicrobials or kill micro-organisms by contact [104, 105]. Various synthetic approaches based on immobilization or the release of bactericidal substances have been extensively explored to produce bactericidal coatings [106, 107]. However, they are not completely satisfactory for biomedical applications because of antibiotic resistance and impairing peri-implant bone growth. A preferred solution is to develop a non-conventional antimicrobial biomolecule composite coating with CaP, which can inhibit bacterial colonization and concomitantly promote osteoblast functions
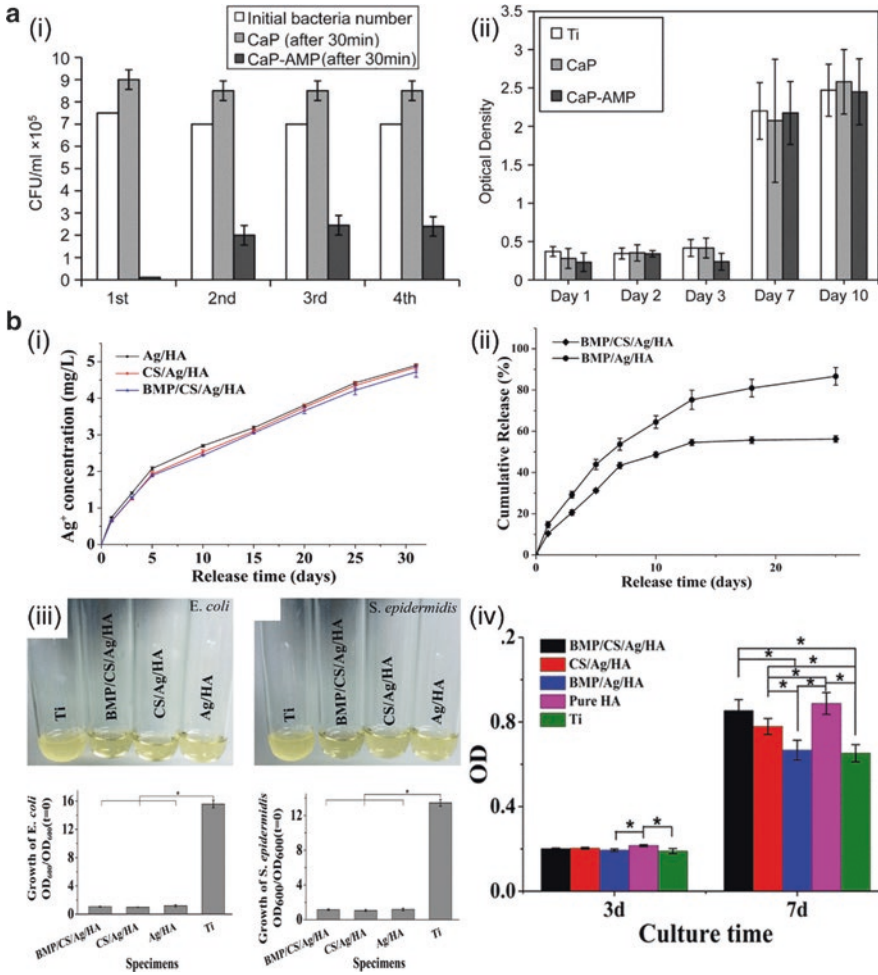
Fig. 6 (**a**) (**i**) Antimicrobial performance of CaP-AMP composite coatings against *P. aeruginosa* for four 30 min cycles. After each 30 min, the samples were rinsed and treated with equal amounts of bacteria for another 30 min. In the first cycle (1st), 100% of bacteria were killed. In subsequent cycles, the killing effect was diminished but efficiently inhibited the bacteria growth. (**ii**) Cytotoxicity (MTT assay) of CaP-AMP with MG-63 osteoblast cells. No statistical difference in cell activity between the CaP-AMP composite coating and the two controls (CaP coating and Ti) after 10 days of incubation [12]. (**b**) In vitro release profiles of (**i**) Ag ions and (**ii**) BMP-2 from different coatings. (**iii**) Suspensions and corresponding optical density measurements of *E. coli* and *S. epidermidis* that were cultured with different specimens for 24 h. (**iv**) Proliferation of bone marrow stromal cells measured by Alamar Blue assay [108]

through its interactions with proteins, bacteria and tissue-forming cells. Kazemzadeh-Narbat et al. [12] developed a CaP-AMP composite coating on a Ti surface, and found that the composite coating has a stable antimicrobial performance to Gram-positive (*S. aureus*) and Gram-negative (*P. aeruginosa*) bacteria, while it showed no cytotoxicity with osteoblast-like cells, as shown in Fig. 6a.

In addition to antimicrobial biomolecules, some antimicrobial elements such as silver (Ag), copper (Cu), Zn, and fluorine (F) can be added to CaP, usually HA, to obtain antimicrobial coatings [13–17]. As one of the most stable antimicrobial agents, Ag could effectively control bacteria adhesion and prevent biofilm formation for its broad antibacterial spectrum and oligodynamic bactericidal activity, and bacterial resistance against Ag is minimal [109]. Many previous studies have revealed that Ag-doped HA coatings [13, 110–112] synthesized through thermal spray [110], magnetron sputtering [112], sol-gel methods [111] and electrochemical deposition [13] have unique antimicrobial properties. However, the release rate of these antimicrobial agents was too fast in one-layer coatings, limiting the anti-infection effects in the early stage of peri-implantation. Multi-layer coatings were preferred to encourage the prolonged release of antimicrobial agents during the implantation [113]. Saidin et al. [114] applied the polydopamine as an intermediate layer for silver nanoparticles and HA immobilization on SS316L, and the Ag$^+$ ions were slowly released up to 7 days, suggesting that a long-term antibacterial activity could be achieved. Because Ag nanoparticles are easy to agglomerate during the coating process, which will lead to a large increase in local Ag concentration and thus potentially affect cell activity, Xie et al. [108] introduced BMP-2 into the Ag nanoparticle contained HA coatings on Ti surfaces by combining electrochemical deposition of Ag and electrostatic immobilization of BMP-2 and a stabilizing agent of chitosan (CS). The multilayered composite coatings can not only realize the uniform distribution and sustained release of Ag nanoparticles to retain the antibacterial activity, but also CS facilitates the immobilization and sustained release of BMP-2 to exhibit high osteoinductivity, as shown in Fig. 6b.

5   Conclusion

In order to obtain specific functionalities on the metallic implant materials for orthopedic applications, surface modifications with CaP coatings are of particular interest and are required in the development of high-performance metallic implant materials. This chapter generally introduces several significant biofunctions of CaP coatings on metallic implant materials. However, while numerous in vitro studies have made great progress their translation to in vivo studies and similar clinical outcomes is not favorable, and the biological performance of CaP coatings differ considerably in terms of composition, microstructure, solubility, thickness, metallic substrate, etc. Therefore, it is necessary to establish the correlation of CaP coating properties to biological response. In addition, much more advanced biofunctions

should be continually explored and loaded on these intrinsically biocompatible coatings to extend their biomedical applications.

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