Biomaterials xxx (2013) 1–10

Contents lists available at SciVerse ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Leading opinion

The future of biologic coatings for orthopaedic implants

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ARTICLE INFO

Article history:
Received 6 January 2013
Accepted 20 January 2013
Available online xxx

Keywords:
Implant coatings
Orthopaedics
Osseointegration
Calcium phosphate coatings
Infection
Foreign body reaction

ABSTRACT

Implants are widely used for orthopaedic applications such as fixing fractures, repairing non-unions, obtaining a joint arthrodesis, total joint arthroplasty, spinal reconstruction, and soft tissue anchorage. Previously, orthopaedic implants were designed simply as mechanical devices; the biological aspects of the implant were a byproduct of stable internal/external fixation of the device to the surrounding bone or soft tissue. More recently, biologic coatings have been incorporated into orthopaedic implants in order to modulate the surrounding biological environment. This opinion article reviews current and potential future use of biologic coatings for orthopaedic implants to facilitate osseointegration and mitigate possible adverse tissue responses including the foreign body reaction and implant infection. While many of these coatings are still in the preclinical testing stage, bioengineers, material scientists and surgeons continue to explore surface coatings as a means of improving clinical outcome of patients undergoing orthopaedic surgery.

1. Introduction

Orthopaedic implants are used routinely worldwide for fixation of long bone fractures and non-unions, for correction and stabilization of spinal fractures and deformities, for replacement of arthritic joints, and for other orthopaedic and maxillofacial applications. The primary aim of these devices is to provide mechanical stabilization so that optimal alignment and function of bone can be maintained during physiologic loading of bones and joints. In this way, the implants facilitate the relief of pain and more normal use of the injured limb or body part, and thus foster earlier return to function. By providing stability to bone fractures for example, orthopaedic implants indirectly assist in the biological aspects of bone healing by decreasing unwanted shear stress [1]. Similarly, devices that minimize micromotion at the bone-implant interface of cementless joint replacements, and unwanted movements between opposed bone surfaces in spinal fusion will enhance bone formation and remodelling [2–4]. The mechanical and biological aspects of bone healing are closely inter-related and ultimately determine final clinical outcome.

Historically, the design of orthopaedic fixation and reconstructive devices has focused primarily on the mechanical properties and function of the implant. In fracture fixation for example, this concept purports that bone will "heal by itself" if appropriately stabilized. However, this approach is shortsighted. Indeed in the USA, there are approximately 600,000 fractures with delayed union and 100,000 cases of nonunion each year [5]. Cementless joint replacements do not always osseointegrate with the surrounding bone, which may lead to implant migration and possible loosening [6]. Spinal fusion is not always a certainty [4].

The ultimate purpose of surgery employing a device is to help obtain, restore, or improve pre-morbid function. This goal may be compromised due to many potential factors including patient characteristics (e.g. chronic systemic metabolic disease, chemotherapy, smoking, excessive alcohol use, diabetes, medications, poor compliance with rehabilitation), local factors (e.g. difficult anatomical site and high degree of comminution of fractures, extensive injury to the soft tissue bed, infection, poor vascular supply, irradiation), and surgical and implant factors (suboptimal bone reduction, surgical technique, or application of the implant, inadequate implant characteristics) [5]. These facts have stimulated research into how the biological milieu of the implant bed could be modulated in order to help ensure a more robust bone healing response. The potential advantages are readily apparent: more vigorous, and expeditious bone healing would allow earlier rehabilitation and return of function. Although systemic pharmacological treatments to accomplish this goal have been considered, local strategies have

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0142-9612/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.biomaterials.2013.01.074

several advantages including local targeted anatomic delivery of one or more biologics to the injury site, lower overall dosage requirements, and mitigation of potentially serious systemic side effects. This review will address strategies to improve bone healing (for example of fractures, non-unions, spinal fusion) and implant osseointegration for joint replacement via local delivery of molecules via implant coatings.

Orthopaedic devices may function in an appropriate fashion mechanically and biologically, however acute and chronic infection are potential dreaded complications that may necessitate further surgery. Infections of orthopaedic fracture and reconstructive devices occur in approximately 5% of cases and total about 100,000 cases per year in the USA alone [7,8]. For primary total hip replacement, the surgical site infection rate varies from about 0.2% to 2.2% [9]. Despite a comprehensive infection surveillance program, the rate of deep surgical site infection for primary hip replacement in the Kaiser Permanente registry in the USA was recently reported to be 0.51% [9]. Infections in spine surgery occur in approximately 2%–5% of cases [10]. Implant infections are a substantial cause of morbidity and even mortality, and are very costly to the patient and society in general [8].

Implant infections are not only a consequence of host factors (such as obesity and chronic medical conditions) and surgical technique [9]. The anatomical site and characteristics of the implanted device including size, shape, material, topography and intended use are important variables [7]. The use of prophylactic systemic antibiotics has been shown to dramatically reduce the incidence of implant related infections [11,12]. However, there are additional opportunities for local delivery of antibiotics and other anti-infective agents. Antibiotic containing bone cements appear to reduce the risk of infection in joint replacement surgery, although this point is controversial [12,13]. Thus there are ongoing opportunities to coat the implant directly with antibiotics or other biomolecules to reduce implant related infections [10,14].

This opinion paper reviews methods to coat prostheses implanted into bone in order to enhance osseointegration and mitigate adverse events associated with the foreign body response or infection. These implants of the future will hopefully modulate the local environment in a favourable manner with minimal risks, to improve patient outcome.

2. Coatings to enhance osseointegration

2.1. Calcium phosphate-like coatings

2.1.1. Mechanism of action and clinical results

Bone is a composite structure composed of cells, protein (mainly collagen and other signalling proteins) and mineral. The inorganic mineral phase of bone constitutes about 50% of its weight and is mainly composed of carbonated hydroxyapatite (HA). Coating the surface with HA has been shown to improve osseointegration of a cementless metallic prosthesis within bone [15,16]. HA is chemically similar to the apatite of the host's bone, and is a source of calcium and phosphate to the bone-HA interface [17]. Sintered HA can form tight bonds with living bone with little degradation of the HA layer. However, suboptimal fatigue properties of sintered HA have lead to the development of thinner coatings (about 30–100 μm) for application to a titanium implant substrate via plasma spraying. Other techniques of HA coating have also been introduced including sputtering, pulse layer deposition and electrostatic multilayer assemblies fabricated using the layer-by-layer technique [18]. The shear strength of HA plasma-sprayed titanium alloy implants in animal models is similar to the shear strength of cortical bone [17]. Osteoblasts form osteoid directly on the HA surface coating, suggesting that the bone-implant interface is bonded both chemically and biologically to the HA. Traditionally, HA coatings have been thought of as osteoconductive. However, calcium phosphate biomaterials with certain 3-dimensional geometries have been shown to bind endogenous bone morphogenetic proteins, and therefore some have designated these materials with osteoinductive properties [19].

HA coatings have been shown to enhance new bone formation on an implant surface with a line-to-line fit, and in situations where there are gaps of 1–2 mm between the coated implant and the surrounding bone. In canine studies, new bone formation was found even at distances of 400 μm from the HA surface, suggesting a gradient effect to the osteoconductive properties of HA [20]. Furthermore, the presence of an HA coating prevents the formation of fibrous tissue that would normally result due to micromovements of an uncoated titanium implant [21].

The bioresorption of HA coatings is still a matter of controversy. The two main methods of resorption include one that is solution mediated (dissolution), and another that is cell mediated via phagocytosis [22,23]. The HA coatings undergo variable resorption which is dictated by numerous chemical, biological and mechanical factors including the composition and physico-chemical properties of the coating, the anatomical location, and whether micromotion is present at the interface with bone [24]. Increased crystallinity appears to slow resorption of HA, and decrease bone ingrowth [25]. Mechanical instability hastens the dissolution of HA [20].

Hydroxyapatite coatings not only provide a mechanism to enhance osseointegration, but function to seal the interface from wear particles and macrophage associated periprosthetic osteolysis [26,27]. The majority of studies of total hip replacement have shown improved fixation with a decrease in the number of radiolucencies around an HA coated titanium alloy femoral component [28,29], although others have shown no differences between coated and uncoated implants [30,31]. A recent systematic review of randomized controlled trials of porous coated femoral components with or without HA in primary uncemented total hip replacement demonstrated no benefit [32]. However, there have been reports of adverse events associated with these coatings, which may fragment, migrate and even cause increased polyethylene wear secondary to third body abrasive wear [33–36]. Many of these adverse events have been found with first generation thicker HA coatings, and may be less relevant to current implants with thinner more uniform HA coatings.

Recently, HA coatings have been used not only for their osteoconductive properties, but as a method for delivery of growth factors, bioactive molecules, and DNA [18,37,38]. For example, HA coatings augmented with bone morphogenetic protein-7 (BMP-7) placed on segmental femoral diaphyseal replacement prostheses improved bone ingrowth in a canine extra-cortical bone-bridging model. Titanium alloy plasma-sprayed porous HA coatings infiltrated with collagen, recombinant human bone morphogenetic protein (rhBMP-2) and RGD peptide improved mesenchymal stem cell (MSC) adhesion, proliferation and differentiation in vitro, and increased bone formation in ectopic muscle and intra-osseous locations in vivo [18]. Another group used hydroxyapatite nanoparticles complexed with chitosan into nanoscale non-degradable electrostatic multilayers which were capped with a degradable poly(β-amino ester) based film incorporating physiological amounts of rhBMP-2 [39]. Plasmid DNA bound to calcium phosphate coatings deposited on poly-lactide-co-glycolide (PLG) were shown to be released in vitro according to the properties of the mineral and solution environment [37]. These methods of delivery of bioactive molecules extend the function of HA as a coating to enhance new bone formation on orthopaedic implants. The biologics added to HA must be introduced at the appropriate time (some are heat

Please cite this article in press as: Goodman SB, et al., The future of biologic coatings for orthopaedic implants, Biomaterials (2013), http://dx.doi.org/10.1016/j.biomaterials.2013.01.074

sensitive) and dose, and their release kinetics from the HA have to be carefully determined for optimal outcome.

2.1.2. Future directions

HA coatings by themselves provide an osteoconductive and (arguably) an osteoinductive approach for enhancement of bone formation on orthopaedic implants. These biological properties may be augmented further by adding growth factors and other molecules to produce a truly osteoinductive platform. Questions related to the necessity and efficacy of HA coatings in different anatomic sites, the robustness of HA coatings to withstand physiological loads without fragmentation, and problems related to third body wear by HA particles limit its more widespread use. Further research to answer these questions will improve the mechanical and biologic aspects of HA coatings and optimize their safety and efficacy.

2.2. Biomolecule coatings

A wide range of biomolecules may be coated on the surface of the implant to promote osteoinduction. Large proteins or glycosaminoclycans such as collagen and chondroitin sulphate provide a biomimetic coating on the surface of an implant which can improve integration once implanted in the body [40,41]. Growth factors are another type of widely used biomolecules for implant coatings due to their ability to modulate cellular functions such as decreasing inflammation, enhancing stem cell differentiation, inducing blood vessel formation, or acting as chemoattractants for circulating osteoprogenitors [42–44]. In addition to using whole protein molecules, small peptides derived from protein molecules may also be used to enhance desirable cellular functions such as adhesion or bone formation from local osteoblasts [45–47]. Compared to the use of whole proteins, the smaller size of the peptides allows potential higher concentration of specific biological cues to be incorporated into the coating. As an alternative of using proteins or peptides, DNA molecules have also been incorporated into implant coatings; these molecules can translocate into the cell nucleus to express sequence specific mRNAs which can produce proteins over the course of one to two weeks [48,49].

To achieve effective osseointegration, it is critical to develop methods to enable efficient loading of biomolecules onto the implant surface as well as modulate the release of such molecules in a controlled manner, while retaining their specific biological functions. The currently available techniques can be broadly divided into three categories including hydrogel coatings, layer-by-layer coatings, and immobilization.

2.2.1. Hydrogel coatings

One of the most widely used methods of coating orthopaedic implants is simply immersing orthopaedic implants into hydrogel solutions that contain biomolecules of interest. The implant is then removed and air dried to allow adsorption of molecules onto the surface of the implant. Given its ease of application, hydrogel coatings have been applied to coat various orthopaedic implants with a broad range of biomolecules including growth factors, viruses and peptides. Titanium implants coated with collagen and chondroitin sulphate lead to increased early bone remodelling around the implant, which is an indicator of increased osseointegration [41]. Another study compared various hydrogels for coating titanium implants with growth factors using collagen, decorin and chondroitin sulphate. The results indicated that a collagen/chondroitin sulphate coating was most effective among the tested groups in enhancing osseointegration [50]. Poly(ε-caprolactone) (PCL) scaffolds coated with adeno-associated viral vector encoding BMP-2 also lead to increased osseointegration and bone formation in rat femoral defects [48]. While the hydrogel coatings are simple to apply and can rapidly coat implants with complex geometry, there is minimal control of loading efficiency or release kinetics, and this method is subject to batch-to-batch variability.

2.2.2. Layer-by-layer coatings

Given that most implant surfaces are hydrophobic and neutral charged, coating implants by simple absorption of biomolecules is often inefficient [51]. To facilitate more effective adsorption of biomolecules, a surface charge may be introduced to the implant surface by plasma etching or modifying with molecules such as heparin The charged surface is more effective at binding growth factors, however, deposition of a large amount of molecules with tailorable release remains a challenge [52]. To address this problem, layer-by-layer (LBL) coatings have been developed, which involves dipping implants repeatedly in polyelectrolyte solutions with opposite charges. To control the loading efficiency and release kinetics of the encapsulated biomolecules, various parameters may be changed including the number of layers, the chemical structure of the polyelectrolytes and the concentration of the biomolecules in solution (Fig. 1).

The LBL technique has been used for the deposition of growth factors on a variety of implant surfaces. Polycaprolactone/β-tricalcium phosphate (PCL/β-TCP) scaffolds coated with BMP-2 via an LBL approach led to enhanced ectopic bone formation in the rat hind limb tissue [42]. Dual growth factor release from an LBL platform may also be achieved by loading different growth factors in different layers to promote desirable cellular processes [53]. To mimic the natural bone healing process, VEGF and BMP-2 were delivered from the surface of PCL/β-TCP scaffolds to stimulate sequential blood vessel ingrowth and bone formation. Dual growth factor delivery resulted in increased bone formation compared to delivery of a single growth factor. The versatility of LBL has been further demonstrated through the sequential deposition of hydroxyapatite and BMP-2 [39]. Hydroxyapatite formed the base layers while BMP-2 was presented in the outermost layers. By controlling the degradation rate and binding affinity of polyelectrolytes, the system was designed to release BMP-2 while the hydroxyapatite layer persisted which promotes proliferation and differentiation of mesenchymal stem cells.

LBL represents a promising technique for effective loading and controlled release of multiple types of biomolecules from the orthopaedic implant surface. Despite its versatility, several barriers remain before LBL can be broadly applied for promoting osseointegration. First, most current platforms require the use of a few hundred layers to avoid a burst release of the biomolecules; thus the LBL method is labour intensive, costly, and may lead to batch-to-batch variability. Second, the LBL coating process was often performed using acidic solution for effective loading, which is not biomolecule friendly. Furthermore, the mechanical stability of the layers upon implantation into the bony defect is another important aspect that should be considered. Future studies that address such limitations would accelerate successful application of LBL platforms for orthopaedic applications. Design of polyelectrolytes may enable high affinity for biomolecule binding at neutral pH using fewer layers. More research is also required on the stability of LBL coatings during implantation e.g. delamination during a press-fit implantation.

2.2.3. Immobilization of signals on implant surface

While controlled release of soluble biomolecules is useful, in some cases, immobilizing biomolecules on the surface of orthopaedic implants may also be desirable to improve osseointegration. Peptides are the most commonly used biomolecule that are immobilized onto orthopaedic coatings. Peptides interact with cells through surface receptors, which trigger downstream responses

Please cite this article in press as: Goodman SB, et al., The future of biologic coatings for orthopaedic implants, Biomaterials (2013), http://dx.doi.org/10.1016/j.biomaterials.2013.01.074

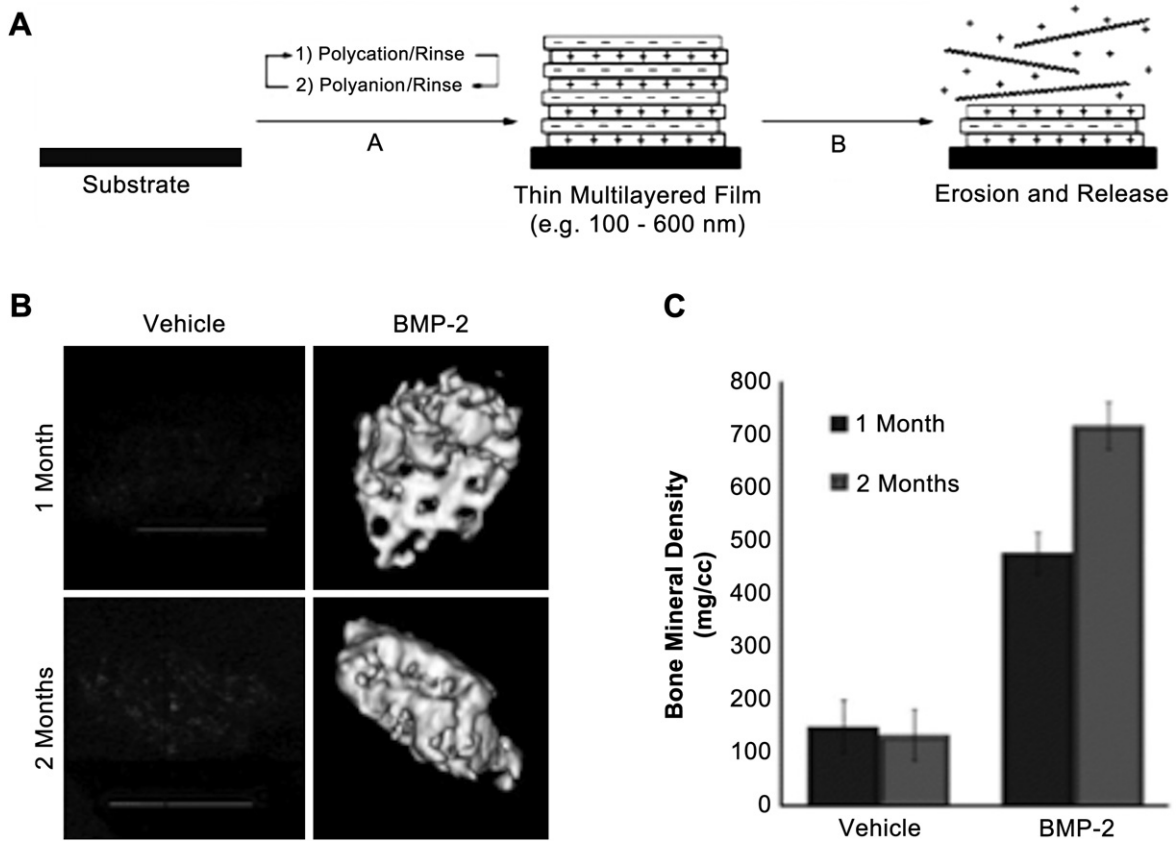

Fig. 1. (A) Layer-by-Layer deposition is formed through the sequential deposition of positive and negative charged polyelectrolytes. Biomolecules are entrapped within the polyelectrolyte layers and are released through degradation of the layers [55] (B) Micro-CT data showing ectopic bone formation following implantation of layer-by-layer coated scaffolds in the hind limbs of mice. Control scaffolds (vehicle) show very little radio opacity indicating that BMP-2 is necessary for bone formation. (C) Quantitative measurement of bone mineral density at the same time points chosen for micro-CT analysis [42]. Images have been adapted from Refs. [42,55].

such as integrin mediated attachment or osteoblast differentiation. GFOGER is one such peptide that is derived from collagen and is known to bind the $\alpha 2\beta 1$ integrin receptor involved in osteogenesis [47]. GFOGER was absorbed on the surface of a PCL scaffold and implanted into femoral defects in a rat model. The peptide coated scaffolds resulted in over 2-fold increase in bone volume at 12 weeks, which confirmed the bioactivity of the coating.

Although peptides can be absorbed onto the surface of polymeric substrates, surface absorption of peptides onto metal surfaces has been largely ineffective. To enhance peptide immobilization on metal surface, stable peptide linkers have been developed utilizing the strong binding affinity between phosphonic acid and titanium oxide. Four phosphonopropionic acids linked together have been conjugated to cyclo(-RGDfK-) peptide with a spacer consisting of three aminohexanoic acids, which provide sufficient distance between the peptide and the implant surface [45]. The functionalized coating significantly improved cell adhesion and was shown to be stable during gamma sterilization. The use of a spacer between the peptide and implant surface increased the mobility of the peptide, and the effects of ligand clustering on titanium implant surface has been investigated [54]. At equal molar ligand concentration, trimers and pentamers of the fibronectin binding domain was more efficient at binding integrin than monomers and dimers. These results suggest that nanoclusters of ligands are more effective for cell adhesion than random distributions. It was also shown that the nanoclusters of trimers and pentamers enhanced osseointegration in vivo in a pull-out test model.

2.2.4. Future directions

Future development of biomolecule coatings will aim to emulate biomolecule function of the host environment. Recent studies have demonstrated the importance of controlled biomolecule delivery matching the natural wound healing response. Sequential delivery of growth factors has been used to separately target blood vessel formation followed by bone formation [53]. Likewise, methods have been developed for the sequential delivery of plasmid DNA from an implant surface [55]. Each biomolecule may be designed to target specific stages in the wound healing process or even modulate adverse events such as un-controlled inflammation. Plasmid DNA or siRNA can play a pivotal role in this wound healing process. The major advantage of oligonucleotide delivery is the ability to specifically regulate intracellular events leading to increased or decreased homologous protein production. One disadvantage however, is the instability of such biomolecule in vivo. The future of this technology will not only depend on the ability to coat such biomolecules on the implant surface but will also depend on the delivery and presentation of bioactive biomolecules. Biomolecule presentation will be of even greater importance for immobilized coatings.

The future development of immobilized coatings will likely utilize mechanisms such as spacers to enhance mobility of the biomolecules and the in vivo functionality. The discovery of peptides with greater specificity for bone formation will also provide new tools for enhancing osseointegration. More extensive research is also required to examine the stability of such coatings during the abrasive implantation procedures.

Please cite this article in press as: Goodman SB, et al., The future of biologic coatings for orthopaedic implants, Biomaterials (2013), http://dx.doi.org/10.1016/j.biomaterials.2013.01.074

3. Coatings to mitigate the foreign body response

3.1. The foreign body reaction to implants or osteoclasts

Bone, like other tissues, responds to acute injury by a series of events that constitute an acute inflammatory reaction. Insertion of an implant of any type within the body including bone evokes an inflammatory and (usually) limited foreign body reaction [56]. During use of an orthopaedic implant, wear particles and other byproducts are generated from the bearing surfaces of joint replacements, and non-articulating implant surfaces that impinge or fret (e.g. screws in a plate for fracture fixation or spinal stabilization). Depending on the anatomic location, the number and characteristics of the wear byproducts and the host's ability to distribute, isolate or detoxify the particles, these wear byproducts may be benign or more harmful. A localized foreign body and chronic inflammatory reaction may occur, resulting in bone destruction, called osteolysis [57]. Research has concentrated on methods to enhance osseointegration of orthopaedic implants using coatings, but few studies have explored coatings to mitigate inflammation directly. This is a crucial subject when discussing drug eluting cardiac stents, which are frequently coated with and elute biologics to modulate local tissue reactions [58,59].

The chronic inflammatory and foreign body response to orthopaedic implant byproducts has been well characterized. Cytokines, chemokines and other proinflammatory molecules are released at the implant interface by polymorphonuclear leukocytes, macrophages, activated fibroblasts and other cells, disturbing normal homeostatic mechanisms [60]. If this process continues without resolution, it results in chronic inflammation and osteolysis, jeopardizing the long-term stability of the implant. Indeed orthopaedic wear byproducts have been shown to stimulate a systemic rather than merely a localized biologic reaction [61]. Interference with the systemic trafficking of monocyte/macrophages (that may become foreign body giant cells and bone resorbing osteoclasts) may be one strategy to mitigate the chronic inflammatory reaction to implants [62]. This work has stimulated considerations to coat orthopaedic implants with bioactive molecules to mitigate the systemic foreign body reaction, specific cytokines/chemokines, or even stimulate migrating osteoprogenitor cells to migrate to the implant site [63].

3.2. Bisphosphonates

Bone constantly undergoes remodelling primarily by proformative osteoblasts and pro-resorptive osteoclasts. These processes occur in the presence of a freshly implanted device and throughout the lifetime of the prosthesis. Bisphosphonates induce apoptosis of osteoclasts, which are derived from the monocyte-macrophage lineage and normally degrade bone [64]. Thus bisphosphonates alter the homeostasis of bone in favour of bone formation over bone resorption. The bisphosphonates attach to the mineral phase of bone and are recycled by the osteoclasts.

Bisphosphonate coatings have been used to enhance implant fixation and bone ingrowth by increasing the local amount of new bone at the implant site. In vitro and in vivo studies have been carried out to determine the elution characteristics and the effects on the surrounding bone [65,66]. Zoledronic acid coating improved bone ingrowth in a canine porous coated implant model [65,66]. Zoledronate grafted onto HA coatings on titanium implants in rat condyles demonstrated dose–response effects on peri-implant bone density [67]. Using stainless steel coated and uncoated screws in rat tibias, an N-bisphosphonate, pamidronate was immobilized onto fibrinogen, and the N-bisphosphonate, ibandronate, adsorbed on top of this layer. Pull-out force (28%) and pull-out energy (90%) were increased after 2 weeks, compared to uncoated screws [68]. A companion study using coated screws in rats found that HA improved bone-implant attachment, whereas the two bisphosphonate coatings together improved fixation by increasing the amount of surrounding bone [69]. A recent study incorporating a rabbit intramedullary tibial rod model examined the peri-implant bone using histomorphometric methods and push-out mechanical tests [70]. Serum bone turnover markers were also measured. Alendronate and hydroxyapatite improved bone-implant contact, bone mass and bone mineral density around the rod. A composite coating of risedronate and hydroxyapatite had similar effects, however this combination had a greater effect on bones remote from the implant.

3.3. Future directions

The innate immune system protects the organism from adverse stimuli that can potentially lead to injury, sometimes terminally. However, acute inflammation also initiates a series of events leading to repair and re-establishment of homeostasis. Clearly, a balance between inflammation and repair must be reached to ensure survival of the organism. Optimally, systems (including implant coatings) should be developed to abort/modulate acute inflammation, avoid chronic inflammation and fibrosis, and initiate the reparative phase concurrently. With regards to orthopaedic implants, bisphosphonates released from surface coatings appear to be a viable method to increase peri-implant bone and overall stability. Whether these effects are temporary or more sustained will have to be determined. Careful dosing requirements must be determined to avoid any adverse systemic effects.

4. Implant coatings to mitigate infection

4.1. Infection of orthopaedic implants

Orthopaedic implant-associated infection (OII) is one of the most common complications associated with devices for fracture fixation, joint replacement and spine surgery. Bacterial colonization and biofilm formation on the implanted device may lead to acute and chronic infection of the underlying bone and the adjacent soft tissues [71]. Biofilm on the implant surface protects the microorganisms from the host immune system and antibiotic therapy [13,72–75] which may lead to persistence of infection despite continued aggressive antibiotic treatment. These events can lead to delayed bone healing or ingrowth, nonunion of fractures, and implant loosening. Treatment often necessitates surgical removal of the device in addition to prolonged courses of antibiotic therapy, both systemic and local. Thus OII is a substantial healthcare burden, and leads to prolonged patient suffering, and substantial morbidity and even mortality.

Free floating planktonic bacteria without a surrounding biofilm that are located in fluids and tissues are normally accessible to appropriate systemic antibiotics. However bacteria adherent to implants are often in large numbers and embedded in an extracellular matrix or "slime" that is hidden from the host's immune system and resistant to antibiotics and detergents [76]. Prolonged use of antibiotics at higher doses to cure such infections may lead to drug resistance systemic and local toxicity, and potentially compromise bone growth, immune system surveillance and implant osseointegration. Such limitations have prompted the development of alternative prophylactic and therapeutic methods to prevent and treat infection, including better physiochemical modification of the biomaterial implant surface and the design of more efficacious coatings on the implant surface.

Orthopaedic implants must be non-cytotoxic and obtain mechanical stability with the adjacent bone and soft tissue. With

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regards to integration of orthopaedic implants, Gristina coined the phrase the "race for the surface," implying that host cells and bacteria compete to adhere, replicate and colonize the implant surface. Ideally, the race is won by host cells, which provide a stable interface with implant integration while "defending" the implant surface from invading bacteria by vigorous immune competence [71].

Orthopaedic devices are expected to stimulate host tissue integration and prevent microbial adhesion and colonization. However, the balance between these two requirements is often challenging. Biomaterial surfaces that facilitate host cell adhesion, spreading, and growth are also favourable to microorganisms that share many of the same adhesive mechanisms as host cells [77,78]. On the other hand, surfaces and coatings designed to prevent bacterial colonization and biofilm formation may not effectively integrate with host tissues. Thus, the challenge is to develop new infection-resistant coatings without impairing local host immune competence or the potential for tissue integration.

4.2. Coatings to mitigate infection

Coatings can be categorized as passive or active depending on whether there are anti-bacterial agents delivered locally. Passive coatings do not release bactericidal agents to the surrounding tissues; these coatings impede bacterial adhesion and/or kill bacteria upon contact. In comparison, active coatings release pre-incorporated bactericidal agents such as antibiotics, antiseptics, silver ions and growth factors/chemokines/peptides to down-regulate infection.

4.2.1. Adhesion resistant coatings (passive coatings)

The surface characteristics of implants such as surface roughness and chemistry, hydrophilicity, surface energy, surface potential and conductivity play crucial roles in initial bacterial adhesion to implants and subsequent biofilm formation. Modification of the physiochemical surface properties of the implant is a relatively simple and economic way to counteract bacterial colonization. For example, ultraviolet (UV) light irradiation can lead to an increase in "spontaneous" wettability on titanium dioxide, which can inhibit bacterial adhesion without compromising osteogenesis on titanium alloy implants [79,80]. A bacterial anti-adhesive surface can also be achieved by modifying the crystalline structure of the surface oxide layer. Studies have shown that the modified crystalline anatase-type titanium oxide layer significantly reduces bacterial attachment without affecting the host cell's metabolic activity [81].

In addition to physiochemical modifications on the biomaterial surface, certain polymer coatings such as the hydrophilic polymethacrylic acid, polyethylene oxide or protein resistant polyethylene glycol can be applied to the surface of titanium implants and result in significant inhibition of bacterial adhesion [82–85]. Although some of these coatings may impair local osteoblast function on the surface of implant, the use of additional bioactive molecules such as sericin and RGD motif with the immobilization technique could restore and even improve the impaired cell function.

Passive coating methods are preferred as long as their anti-bacterial ability is strong enough to prevent biofilm formation. However, the effectiveness of passive coatings for decreasing bacterial adhesion is limited and varies greatly depending on the bacterial species [72]. Alternatives to traditional surface-modifying preventive approaches are needed. Recent studies have reported a new generation of anti-adhesive, antimicrobial coatings that are biosurfactants and microbial amphiphilic compounds [86,87]. However, their use has been limited by their relatively high production cost and technical difficulties of binding them to the implant surface.

4.2.2. Coatings with antibiotics

Prophylactic systematic antibiotics are administered routinely to patients who receive an orthopaedic device in order to prevent peri-operative infection. However, systemic administration of antibiotics has many potential disadvantages including relatively low drug concentration at the target site and possible systemic or organ specific toxicity. Thus, local administration of antibiotics from implants has attracted much attention. Buchholz et at. first popularized the incorporation of antibiotics into polymethylmethacrylate (PMMA) bone cement for local antibiotic prophylaxis in cemented total joint arthroplasty [88]. Other porous materials for antibiotic delivery have included cancellous bone [89], and collagen sponges [90]. Clinical studies have shown that antibiotic loaded bone cement can decrease deep infection rates of cemented total hip arthroplasties, and revision rates due to supposed "aseptic" loosening when combined with systemic antibiotic administration [91]. With the increasing use of cementless implants worldwide, the use of antibiotic loaded bone cement has diminished dramatically, providing a unique opportunity for the development of new anti-bacterial technologies.

Gentamicin, a member of the aminoglycoside antibiotic family has a relatively broad anti-bacterial spectrum and is thermostable. Gentamicin is one of the most widely used antibiotics both in antibiotic loaded cement and antibiotic loaded coatings on titanium implants [13,92]. Other antibiotics with broad anti-bacterial spectra, e.g. cephalothin, carbenicillin, amoxicillin, cefamandole, tobramycin, and vancomycin have been used in bone cement or in coatings of orthopaedic implants [93,94].

Calcium phosphate cements, which are known to be osteoconductive, have been used as carriers for antibiotics and other bioactive molecules [95,96]. Antibiotics such as gentamicin, vancomycin and others have been loaded into porous hydroxyapatite (HA) coatings on titanium implants [92]. The antibiotic-HA-coatings exhibit significant improvement in preventing infection compared with standard HA coatings in vivo [92], but there are still many unresolved issues regarding the methodology of antibiotic incorporation into the HA coating and the optimal release kinetics. With some materials, antibiotics cannot be incorporated into the calcium phosphate coatings because of the extremely high processing temperatures such as those encountered during the plasma spraying procedure. Moreover, physical absorption of antibiotics and other molecules onto the surface of calcium phosphates limits the amount loaded and release kinetics. Antibiotic loading by a dipping method leads to a burst release of the antibiotics, such that more than 80–90% of the antibiotics are released from the calcium phosphate coating within the first 60 min [94,97].

Besides calcium phosphate, biodegradable polymers and sol–gel coatings are also utilized to form controlled release antibiotic-laden coatings on titanium implants. The release of the antibiotics from these new biodegradable coatings is slower than that from HA coatings. The layer-by-layer self-assembly coating technique can also significantly slow the release of antibiotics [98,99]. However, the elution kinetics of antibiotics from the coating is still very fast and currently this method has not been translated to the clinic easily [100]. The ideal antibiotic delivery coating should release antibiotics at optimal bactericidal levels for a sufficiently long period of time to prevent potential infection, and then subsequently antibiotic release should cease quickly to eliminate the risk of developing antibiotic resistance. In addition, any untoward effects of antibiotics on tissue integration of the implant should be minimized [101].

4.2.3. Silver impregnated coatings

Considering the large risk of antibiotic resistance associated with antibiotic loaded coatings, non-antibiotic agents in the coating

Please cite this article in press as: Goodman SB, et al., The future of biologic coatings for orthopaedic implants, Biomaterials (2013), http://dx.doi.org/10.1016/j.biomaterials.2013.01.074

become very attractive alternatives. Among the various dopants, silver is the most well known agent due to its inhibition of bacterial adhesion, broad anti-bacterial spectrum (both gram-negative and positive bacteria) long lasting anti-bacterial effect, and its propensity for being less prone to the development of resistance. Furthermore, silver impregnated coatings are easy to apply and stable using a variety of well-established techniques such as plasma immersion ion implantation (PIII) and physical vapour deposition (PVD) [102,103]. Other less commonly investigated inorganic antimicrobial agents such as copper, fluorine, calcium, nitrogen and zinc have been studied using titanium implants. Silver-containing HA coatings on titanium can effectively inhibit bacterial adhesion and growth without compromising the activity of osteoblasts and epithelial cells [102,104]. Silver-coated titanium screws can prevent implant-associated deep bone infection when they are anodically polarized [105,106]. Though silver shows attractive characteristics as an anti-bacterial dopant for titanium implants, further information is needed regarding its long-term tissue toxicity, the potential acquisition of resistance and the exact mechanism by which bacterial adhesion and growth are inhibited.

4.2.4. Other coatings (organic agents, bioactive molecules, cytokines/chemokines)

Some organic antimicrobial agents such as chlorhexidine, chloroxylenol, and poly-hexamethylenebiguanide have demonstrated efficacy and might be an alternative to avoid the risk of drug resistance. Chlorhexidine can be adsorbed to the TiO_2 layer on titanium surfaces and is released gradually over several days [107]. Its release pattern is similar to that of antibiotic-laden coatings with an initial rapid release rate followed by slower but sustained release [108].

Some bioactive molecules like hyaluronic acid and chitosan possess the ability to prevent bacterial adhesion and/or bactericidal proliferation and activity [109,110]. Although these substances sound very attractive for implant coatings, there is still insufficient in vivo evidence indicating that these bioactive molecules films support osseointegration compared with other coatings like calcium phosphate [111]. Indeed, one report showed that osteoblast adhesion is impaired by the presence of the hyaluronic acid chains [110].

In the early stage of infection, macrophages constitute the primary line of innate immune defence against most bacterial pathogens, and play an essential role in the late cell mediated immune response. Local injection of activated macrophages significantly reduces the mortality of patients with infection [75,112]. In order to perform the innate immune function, macrophages must be recruited to the site of infection and therefore, the local chemoattractant gradient must favour macrophage infiltration [113]. Among all the macrophage-recruiting chemokines, macrophage chemotactic protein one (MCP-1) is the most important for monocyte/macrophage recruitment in infection and inflammation [114]. In order to attract macrophages to the site of infection, one possible strategy is to design a nano-coating system which delivers essential chemoattractant proteins such as MCP-1, IL-12 and others to the local site [115]. One study using an open fracture model in rats demonstrated that the local application of MCP-1 and IL-12 through nano-coating on intramedullary stainless steel Kirschner wires significantly prevented infection [115]. However, recruited and activated macrophages can also synthesize and release proinflammatory cytokines that may lead to further tissue destruction. Also, the kinetics of controlled release of the cytokines from the coating is challenging. Additional in vivo studies investigating the optimal release kinetics and time course are required to evaluate these local nano-coating systems in the treatment of infection.

4.3. Future directions

4.3.1. Immobilization of anti-bacterials for long-term release

Due to the relatively short releasing profile and potential development of pathogen resistance of controlled antibiotics/bioactive molecules releasing coatings, there is increasing interest in immobilization of antibiotics/antimicrobial peptides to the implant surface by permanent covalent tethering for long-term prevention of implant-associated infections [10]. Unlike other non-covalent elution coating systems, covalently immobilized antibiotics such as vancomycin can be permanently tethered to the implant surface and therefore could remain functional over the lifetime of the coating. This may be beneficial by decreasing local and systemic toxicity, as well as antibiotic resistance. Despite the advantages for non-eluting systems, this concept is limited by the fragility of the coatings and killing activity potential of bacteria which might not be directly adjacent to the implant. The best use of such systems might be in combination treatments that include systemic or locally delivered antibiotics.

4.3.2. Multifunctional coatings

Osseointegration is very important to the success of orthopaedic devices implanted within bone. However, biomaterial surfaces that facilitate host cell adhesion, spreading, and growth also favour similar processes by bacteria. Infecting microorganisms share many of the same adhesive mechanisms as host tissue cells, such as extracellular matrix protein fibronectin (Fn) [77]. This molecule is frequently used to coat implants to improve the immobilization rate of antibiotics/antimicrobial peptides, but can also be recognized by Staphylococci by its Fn-binding proteins [78]. On the other hand, surfaces and coatings designed to inhibit bacterial colonization frequently do not effectively integrate with host tissues. Recently, the concept of multiple functionalities for surface coating of implants has been explored [104,116–119]. However, this approach is still in the initial stage of development. These multifunctional coatings should be easily applied, efficacious, have optimal temporal and dosing release profiles, demonstrate no local and systemic toxicity, not interfere with (or possibly even facilitate) adjacent tissue integration and be cost-effective. While no one strategy has dominated the marketplace, active ongoing research will undoubtedly produce a coating technology that will mitigate the occurrence of commonly found implant infections.

5. Discussion and conclusion

The use of orthopaedic implants has grown dramatically in all subspecialities in orthopaedic surgery. These mechanical devices are used routinely to stabilize fractures, non-unions, and arthrodeses, for reconstruction of arthritic joints during total joint arthroplasty, for correction of spinal deformities and in other orthopaedic conditions. Recently, the coating of implants has engendered much interest in order to improve osseointegration, and prevent adverse tissue reactions such as infection, inflammation, the foreign body response and other events.

If osseointegration is a desirable goal, coating the implant with a thin layer of hydroxyapatite (HA) has been shown to be highly efficacious. The composition, location, thickness, uniformity and other physico-chemical variables are important determinants of the efficacy and robustness of the HA coating. Shed particles can be abrasive and act as a generator of third body wear, for example of the softer polyethylene in total joint replacements. Because of this fact, the high degree of integration of currently used porous coated implants, and issues related to cost, HA coatings have not been uniformly adopted worldwide. This area has spawned interest in

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osteoinductive coatings to optimize the implant–tissue interface and enhance osseointegration, especially in more challenging clinical scenarios in which the host bone is not optimal (e.g. previous local infection or irradiation, extensive trauma to bone and soft tissue). Various growth factors and other molecules, primarily proteins, are currently being examined as additives to coatings. This research is still in the experimental phase, as there are numerous questions concerning which molecules should be incorporated in the coating and the method, dosage and optimal time course for delivery. The molecules released from the coating should be targeted to a specific biological process and be efficacious with no toxicity both locally and systemically. The carrier for the active biologic should be biodegradable, and the mechanical and release kinetics of the construct clearly understood. The carrier itself should not interfere with osseointegration of the implant. Furthermore the combination device should be able to be manufactured in a highly reproducible, cost-effective manner. As all potential biomolecules within coatings degrade with time, issues related to storage and delivery must be solved. Finally, if these coatings are to be used clinically, surgeons must be familiar with the indications, contra-indications, potential side effects and complications of coated implants, as well as how to insert or otherwise use the coated implant to optimize patient outcomes. Governmental agencies and insurance carriers must also be involved in the approval process to help ensure that the end product is safe, efficacious and cost-effective.

Perhaps the most needed implant coating technology today relates to the prevention and treatment of deep infection. Implant-associated infection is one of the most common and dreaded complications of reconstructive orthopaedic surgery, and generally necessitates debridement and removal of the implant for eradication of infection. Coatings with metallic ions are currently in the marketplace. However, similar questions as to those posed for biologics arise when antibiotic coatings are considered. Specificity, dosage, release kinetics, stability, biodegradation, delivery and other factors are of great importance. In addition, issues related to local and systemic antibiotic toxicity, antibiotic resistance, alteration in the local microbiologic flora, and the potential emergence of super-infections makes this area of research both highly relevant and controversial. Preclinical in vitro and in vivo studies will prove to be very important prior to clinical use. One bright spot is the great success of antibiotic loaded polymethylmethacrylate bone cement as a prophylactic and therapeutic method of delivery of high doses of antibiotics locally.

In conclusion, researchers, surgeons and manufacturers have only begun to explore the numerous possibilities of local delivery of biologics coated on orthopaedic implants. Based on an assessment of current clinical needs, coatings of devices would be most useful in the prevention and treatment of implant-associated infection, and in complex clinical scenarios in which the implant bed is potentially more hostile than normal such as in cases with previous infection, irradiation, extensive trauma or revision surgery. In addition, if implant coatings could facilitate earlier and more robust osseointegration, patients might be able to return to work and their activities of daily living in a more timely manner. As with other combination devices, coated implants must be shown to be safe, efficacious and cost-effective prior to subsequent adoption and widespread usage.

Acknowledgements

This work has been funded in part by NIH grants 2R01AR055650-05 and 1R01AR063717-01 and the Ellenburg Chair in Surgery, Stanford University (SBG), and the McCormick Faculty Award and Bio-X Interdisciplinary Initiative Grant (FY).

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Please cite this article in press as: Goodman SB, et al., The future of biologic coatings for orthopaedic implants, Biomaterials (2013), http://dx.doi.org/10.1016/j.biomaterials.2013.01.074