

Review

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Review

Peptide-Based Biomaterials for Osteochondral Tissue Regeneration

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Abstract: The healing of osteochondral defects (OCD) resulting from injury, osteochondritis, or osteoarthritis in middle- and old-age individuals, bearing lesions in the cartilage and bone, pain, and loss of joint function, presents challenges to the clinical practitioners because of non-regenerative cartilage and the limitations of current therapies. Bioactive peptide-based osteochondral (OC) tissue regeneration is becoming more popular because it does not have the immunogenicity, misfolding, or denaturation problems associated with original proteins. Periodically, reviews are published on the regeneration of bone and cartilage; however, none of them address the simultaneous healing of these tissues in the complicated heterogeneous environment of the OC interface. As regulators of cell adhesion, proliferation, differentiation, angiogenesis, immunomodulation, and antibacterial activity, potential therapeutic strategies for OC defects utilizing bone and cartilage-specific peptides should be examined and investigated. Therefore, the main goal of this review is to study how they contribute to the healing of OC defects, either alone or in conjunction with other peptides and biomaterials.

Keywords: osteochondral; osteogenic; chondrogenic; cartilage; peptide-based; biomaterial

1. Introduction

An articulating joint's osteochondral (OC) unit comprises the vascularized, mineralized subchondral bone and the acellular, avascular hyaline cartilage connected by a seamless interface.[1] The structural heterogeneity of the OC tissue arises from its diverse organic (cells, aggrecan, collagen) and inorganic (hydroxyapatite) components, along with their spatial orientation, forming gradients from the superficial cartilage to the subchondral bone via middle, deeper, and calcified layers (Figure 1). Cartilage exerts cushioning effects on joint bones and prevents damage from the physiological load; however, an injured cartilage cannot spontaneously regenerate. OC defects (OCD) are created by a variety of biological (aging, osteochondritis, osteoarthritis) or mechanical (accidental trauma, sports injury, prolonged wear) factors, characterized by cartilage and bone lesions, severe joint pain, and loss of joint function. They are more common in the middle-aged and older population. The World Health Organization estimates that 595 million people worldwide or 7.6 percent of the world's population suffered from osteoarthritis alone in 2020. This number has increased by 132.2 percent since 1990. [2]

When cartilage is damaged, the body's natural healing process is triggered by an inflammatory response, which leads to excessive production of reactive oxygen species (ROS) and matrix metalloproteinases (MMPs), further deteriorating the cartilage matrix and eventually inducing osteoarthritis. The treatment of OCD can be palliative (e.g., chondroplasty or microfracture), reparative (fixation), or restorative (autologous chondrocyte implantation (ACI), autologous matrix induced-chondrogenesis (AMIC), osteochondral autograft transplantation (OAT)) with their advantages and limitations.[3–6] Unfortunately, none of these techniques can fully repair the damaged tissue or form hyaline cartilage instead of fibrocartilage. [7]

OC tissue engineering (TE), which combines cells, scaffolds, and biomolecules to mimic extracellular microenvironment, seems promising for regenerating a functional OC tissue. The cells can be used for this purpose are bone marrow- or adipose-derived mesenchymal stem cells (MSCs), osteoblasts and chondroblasts derived through differentiation of MSCs, autologous chondrocytes, or MSCs cocultured with chondrocytes.[8] Scaffolds can be fabricated from various extracellular matrix (ECM)-mimetic biopolymers and synthetic polymers using solvent casting, freeze-drying, electrospinning, microfluidic-based methods, and three-dimensional (3D) printing. Considering heterogeneity of the OC tissue, a bi-layer or multilayer design is usually preferred over injectable hydrogels or single-layered scaffolds, since they possess osteoblasts-seeded porous bone layer forming continuous gradient with nonporous cartilage layer seeded with chondrocytes. Bioactive molecules, such as drugs (e.g., alendronate, dexamethasone), drug-like molecules (e.g., kartogenin, berberine), growth factors or peptides derived from them, are often incorporated into the scaffolds forming smart materials with enhanced regenerative capacity, facilitating cell migration, osteogenic or chondrogenic activity.[9,10] The transforming growth factor- β (TGF- β), bone morphogenetic proteins (BMPs) (especially BMP-2, BMP-4, and BMP-7), stromal cell-derived factor-1 α (SDF-1 α), insulin-like growth factor (IGF) (IGF-1 and IGF-2), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) are the major growth factors which promote MSCs, osteoblasts or chondrocytes recruitment, proliferation and differentiation, vascularization and maintenance of cartilage homeostasis. However, regulating their target selectivity, dose selection, release kinetics, and spatial distribution is quite challenging.

However, bioactive peptides are short-chain amino acid sequences that mimic signaling or binding domains of larger proteins and create a biomimetic environment for recruiting host cells, while controlling their activity and differentiation. They are either delivered alone or combined with biomaterials for tissue regeneration [9]. For instance, peptides either derived from ECM proteins or growth factors, or mimic their function, exhibit selective cells affinity, enhance cell penetration, or form hydrogels through self-assembly were investigated for OC regeneration. They are more effective, stable, scalable, and affordable than large proteins and also, they do not experience issues like immunogenicity, protein folding, and denaturation.[11]

Several reviews have been published highlighting the last five years' clinical and experimental data on bioactive peptides for bone and cartilage regeneration as well as usage of peptide-enhanced bone graft substitutes. [11–14] However, none of them has focused specifically on the recovery of OC defects. Given that peptides could promote cell adhesion, motility, membrane penetration, immunomodulation, and antibacterial activities, besides inducing chondrogenic, osteogenic, and angiogenic differentiation, the primary focus of this review is to highlight their role in healing of OC defects when used alone or in combination with other peptides or biomaterials. Peptides belonging to different subcategories for bone and cartilage regeneration have been discussed after a brief review of the heterogeneity of the OC unit and the prerequisites for OC regeneration. Peptides that aid in osteo-, angio-, or chondrogenic activity, such as adhesion and migration of reparative cells, the creation of a 3D matrix, or an in vivo environment free from infection or inflammation, are covered in the following section. The review concludes with a summary and outlook after summarizing the results of several in vitro and in vivo studies using peptide-conjugated biomaterials.

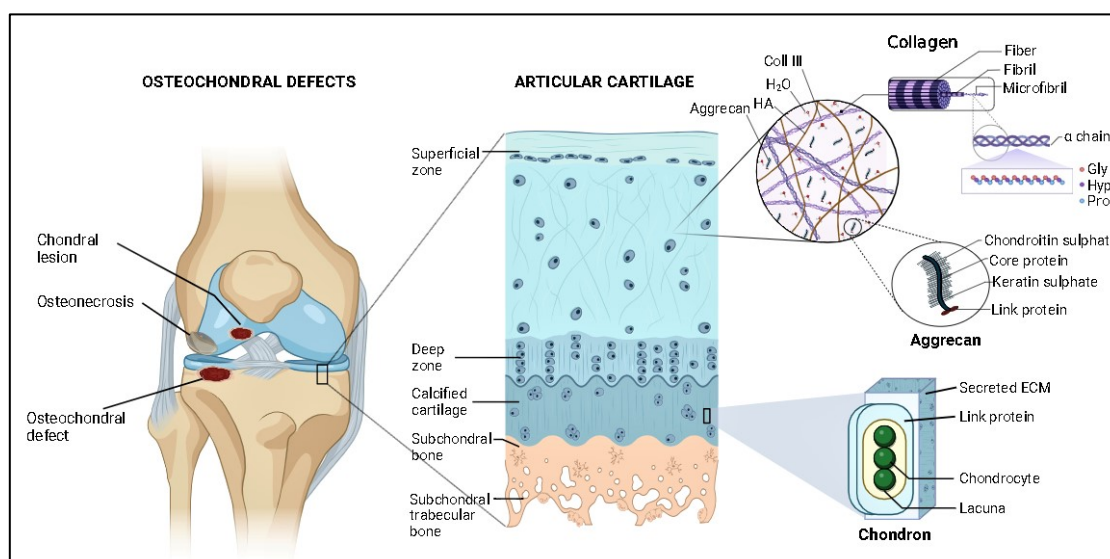


Figure 1. Diagram of the osteochondral unit showing the structural hierarchy, zonal arrangements, and extracellular matrix composition of the articular cartilage. (figure generated via biorender.com).

2. Requirements for Osteochondral Tissue Regeneration

Successful recovery of OC defect faces significant challenge in reproducing the heterogeneous structure of the OC tissue. The present goal of OC regeneration is reviving the basic tissue structure and function under clinical settings, particularly in growth plate defects, cartilage defects in load-bearing sites, or full-thickness OC defects. The prerequisites are native tissue mimetic scaffolds, host tissue mimetic regenerated tissue and a well-controlled inflammatory state to counter MMPs-mediated irreversible destruction of cartilage matrix. The existing platelet-rich plasma (PRP) and exosomes-based therapies greatly passivated MMPs activity. Stem cell therapy maintained cytokine levels by expressing growth factors and limiting production of inflammatory cytokine, such as tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6).[15] Treating with the recombinant IL-1 receptor antagonists and monoclonal antibodies against TNF- α can generate a favorable cartilage microenvironment, which suggests MSCs and drug therapy may complement each other. Genetic engineering aims state reversal by transfecting seed cells with bone/cartilage-specific genes and arthritis inhibitory genes, thus ensuring necessary cytokines production.

Although tissue engineering holds promise for simultaneous bone and cartilage regeneration, injectable hydrogels and monolayer scaffolds fail to replicate the intricate spatial distribution of biochemical cues, particularly at the bone and cartilage interface.[16,17] Advanced techniques such as 3D printing or 3D bioprinting enable customized scaffold fabrication in terms of structure, anisotropy, and cell distribution; however, they involve high cost and intricate setup.[18]

Two transcription factors, Sox9 and Runx2, are essential for converting MSCs into chondrocytes and subsequent transformation into the hypertrophic phenotype, [19,20] while FGFs and BMPs are necessary for triggering bone formation.[21] Despite osteogenic and chondrogenic activity, BMPs have less control over chondrocyte hypertrophy and mineralization.[15,22] Localized delivery of bioactive peptides inducing target protein expression could be an ideal choice for biomimetic bone and cartilage regeneration, avoiding risks associated with growth factor or cell delivery. Adhesion and affinity peptides can be used to promote specific cell attachment and motility, respectively, while chondrogenic and osteogenic peptides can be delivered through multilayered scaffolds to accomplish site-specific differentiation. An antimicrobial peptide can potentially resist bacterial colonization at the defect site. On the other hand, inflammation or immunogenicity can be reduced using penetration peptides which enable selective cargo delivery to the cells and induce macrophage polarization.

3. Peptides for Bone Regeneration

The natural bone healing occurs in two different pathways: intramembranous ossification and endochondral ossification [23]. The former involves direct differentiation of MSC into osteoblasts, which then deposits mineralized matrix in flat bone. The latter is a complicated multi-step process of long bone formation that starts with inflammation and continues with hematoma development, platelet-mediated cytokine release, stem cell and fibroblast migration, chondrogenic differentiation, formation of fibrocartilaginous matrix (soft callus) and then mineralization into woven bones following chondrocyte hypertrophy. The woven bones develop into mature lamellar bone through remodeling and neovascularization. During this process, a variety of cytokines with distinct roles are released, including TGF- β 1, PDGF-1, BMPs, VEGF-1, FGF, SDF-1 α , TNF- α , Chemokine (CC-motif) ligand 2 (CCL2), IL-1b, IL-6, and Wnt proteins.[24] Among these, BMPs, TGF- β 2, and - β 3 play a crucial role in stem cell differentiation by causing hypertrophy and mineralization, while VEGF and angiopoietins promote neoangiogenesis.[25,26] BMP-2, 3, 4, 7, TNF- α , interferon- γ (IFN- γ), and certain hormones regulate the remodeling phase.[27] Since bioactive peptides follow similar cell signaling pathways with these proteins (Figure 2a), and may be beneficial for both in vitro and in vivo bone formation, they are grouped into two categories based on their role: osteo-inducers and angiogenic.

3.1. Osteo-Inducers

3.1.1. Collagen-Mimetic/Derived Peptides

Collagens are a superfamily of proteins consisting of 46 distinct polypeptide chains that supramolecularly assemble into 28 different types of fibrils, fibril-associated with interrupted triple helices (FACIT) and nonfibrillar forms that provide structural support and encourage cell adhesion via integrins. Peptides derived from integrin-binding motifs of collagen type I, the most significant ECM protein, are GFOGER, P15, KOD, DGEA, and BCSP1, which can promote osteogenic activity and in vivo bone formation.

Collagen-mimetic GFOGER (Gly-Phe-Hyp-Gly-Glu-Arg) peptide, derived from collagen α 1 chain, selectively promotes α 2 β 1 integrin binding required for osteoblastic differentiation. [28] Besides improving cell attachment, GFOGER successfully induced in vitro osteogenic differentiation and in vivo bone healing. [28–32] GFOGER coating on synthetic PCL scaffolds remarkably enhanced bone formation in critically sized segmental defects in rats by stimulating osteoblast adhesion and differentiation (Figure 2b). [31] P15, a 15-mer peptide (Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val), derived from collagen type I α 1 chain, has a strong affinity for the cell surface α 2 β 1 integrin receptors. By releasing growth factors and cytokines, the peptide dramatically enhanced the osteogenic differentiation of MSCs.[33] The commercially available P15 formulations significantly enhanced regeneration of alveolar bone and tibial defects in osteoporotic dogs. [34] [35] The collagen-mimetic KOD peptide, made of three units: ((PKG)₄-(POG)₄-(DOG)₄), forms hydrogel through self-assembly inducing platelet activation and blood clotting associated with hematoma formation. [36] POG-based poly-amphiphilic hydrogels allowed faster recovery (within two weeks) of intervertebral disc defects in rabbits due to a significant increase in ECM deposition.[37] DGEA (Asp-Gly-Glu-Ala) derived from collagen type I adhesive motif serves as a crucial ligand for osteoblast differentiation. [38] DGEA-containing PA hydrogels seeded with hMSCs substantially upregulated osteogenic markers (OCN, RUNX2, and ALP). [39]

Using bone and cartilage stimulating peptide (BCSPTM-1 or NGLPGPIGP) present in human collagen type-I, proliferation of rat bone marrow derived osteoblasts and human or bovine chondrocytes was drastically improved with enhanced bone mineral density (BMD) and bone mineral content (BMC) in male Wistar rats.[40] Three highly osteogenic peptides (GPAGPHGPVG, APDPFRMY, and TPERYY) derived from tilapia scale collagen hydrolysate notably increased the MC3T3-E1 cell proliferation, and mineralization activity (ALP synthesis, osteogenic-related gene expression) at concentrations of 50 μ g/mL.[41]

3.1.2. BMP-Mimetic/Derived Peptides

As members of the TGF- β superfamily, BMPs are primarily produced by endothelial cells, osteoblasts, and hypertrophic chondrocytes and can recruit MSCs to the site of injury, differentiate into osteoblasts, while inducing ectopic bone formation.

KIPKASSVPTELSAISTLYL peptide, derived from the knuckle epitope of BMP2, increased ALP activity of osteoprogenitor cells.[42] P24, a BMP-2 mimetic peptide, with 24-mer peptide (Ser-Lys-Ile-Pro-Lys-Ala-Ser-Ser-Val-Pro-Thr-Gly-Leu-Ser-Ala-Ile-Ser-Thr-Leu-Tyr-Leu-Asp-Asp-Asp), bearing the knuckle epitope of the protein that facilitate binding with BMP receptors. P24 successfully induced ectopic bone formation in rodents.[43–45] PEP7 peptide (CKIPKPSSVP-TELSAISMLYL) derived from BMP-2, promoted adhesion, proliferation, and differentiation of MG-63 cells, besides new bone formation in supra-alveolar peri-implant defect model in micropig mandible[46]. BMP peptide (KIPKASSVPTELSAISTLYL), derived from BMP2, increased ALP activity, an early marker for bone formation, in murine osteoprogenitor cells [47] and other cell types, [48–52] besides dose-dependent healing of rabbit radial bone-defects. [53] The other osteoinductive or osteogenic peptides derived from BMP-2 (NSVNSKIPKACCVPELSAI, KIPKASSVPTELSAISTLYL, DWIVA) produced differential effects on in vitro osteogenic differentiation as well as ectopic or orthotopic bone formation in vivo.[12] Bone-forming peptide (BFP-2) with VEHDKEFFHPRYHH sequence, isolated from the immature BMP-7 precursor, triggered osteogenic differentiation of BMSCs, while induced ectopic bone formation after subcutaneous implantation of BFP-2-treated BMSCs in mice (Figure 2c).[54] Similarly, effects of various osteoinductive peptides derived from BMP-4 (RKKNPNCRRH), BMP-7 (TVPKPSSAPTQLNAISTLYF, GQGFSYPYKAVFSTQ, ETLDGQSINPKLAGL), BMP-9 (KVGKACCVPTKLSPISVLY) have been reviewed. [55] Casein kinase 2 (CK2) related peptide has great influence on cell proliferation, and apoptosis, it facilitates in vivo bone formation by interacting with BMP receptor type Ia (BMPRIa).[56] Three BMP-2 mimetic peptides, CK2.1, CK2.2, and CK2.3, triggered the BMP signaling pathways by inhibiting CK2 binding to BMPRIa. [57] C2C12 cells, treated with CK2.3 peptide resulted in osteogenesis, while CK2.2 led to both osteogenesis and adipogenesis. [56,58]

3.1.3. Hormone-Derived Peptides

Parathyroid hormone (PTH) is a major regulator of mineral homeostasis. Parathyroid hormone (PTH)-related peptides, called Teriparatide, which is 1–34 peptide domains of PTH (PTH1–34), stimulated osteoblast activity and increased bone density at the fracture site, leading to healing of non-unions. [59–63] On the other hand, endogenous PTH-related protein (PTHrP) analogues, PTHrP1–34, PTHrP1–36, and PTHrP107–111, increased osteoblast activity and local bone formation.[64–66] Calcitonin gene-related peptide (CGRP) is a 37-mer neuropeptide, having two isoforms: α and β -CGRP. They have been found to stimulate the proliferation and differentiation of osteoprogenitor cells, [67–70] production of osteogenic molecules like IGF-I, BMP-2, [71,72] and reparative bone formation. [73]

3.1.4. Circulating Peptides

Osteogenic growth peptide (OGP), a 14-mer peptide occurring in mammalian blood, increases bone formation through anabolic effects on bone cells [74,75] and differentiation of osteoprogenitor cells leading to upregulated osteogenic markers, including mineralization [76–78] Thrombin peptide 508 (TP508) or Chrysalin is a 23-amino acid peptide, receptor binding domain of thrombin, which enhanced the proliferation, differentiation, and chemotaxis of human osteoblasts [79,80] and VEGF-stimulated angiogenesis [81]. TP508 injected into the fracture gap promoted fracture healing and increased blood vessel formation [82–84].

3.1.5. Other ECM-Derived Peptides

Signaling domains on ECM protein chains, capable of interacting with cell membrane receptors. Various peptides (e.g., FN III9-10/12-14) derived from fibronectin (FN), have shown to promote

osteoblast activity and mineralization, [85] rabbit calvarial defects healing, [86] and augmented BMP-2 and PDGF-BB activities for bone regeneration in vivo. [87]

Collagen-binding motif (CBM) is a cleavage product of osteopontin (OPN) that can specifically bind to collagen [88] and promote migration and osteogenic differentiation [89], bone formation in rabbit calvarial defect model.[90] SVVYGLR (Ser-Val-Val-Tyr-Gly-Leu-Arg) peptide adjacent to the RGD sequence in OPN significantly enhanced the adhesion and proliferation of MSCs, neovascularization, upregulation of osteogenesis and angiogenesis when delivered through a collagen sponge. [91–93] FHRRIKA (Phe-His-Arg-Arg-Ile-Lys-Ala), a cell-binding and heparin-binding domain of bone sialoprotein (BSP) exerts favorable effect on osteoblast adhesion, spreading and mineralization [94] Higher cell proliferation and viability was observed on rat calvarial osteoblasts seeded scaffolds containing the RGD and FHRRIKA sequences.[95]

3.2. Angiogenic

Vascularization is a crucial process during natural bone formation. Many peptides are derived from angiogenic growth factors (e.g., VEGF, FGF-2, PDGF, etc.), ECM (e.g., OPN, ON) and other proteins that have crucial roles in blood vessel formation [96].

VEGF-mimicking QK or KLT peptide (KLTWQELQLKYKGIGGG), derived from the VEGF receptors binding domain 17–35, not only induce endothelial cell migration and proliferation, but also to trigger other complex processes like chemotaxis, capillary sprouting and organization similar to VEGF [97]. PDGF-BB derived PBA2-1c peptide interacts with α - and β -PDGF receptors. Though it's in vivo proangiogenic activity is still unclear, it functions similarly to PDGF in establishing mature blood vessels that are created by VEGF [98]. Exendin-4, a glucagon-like peptide 1 (Glp-1) analogue, stimulates human umbilical vein endothelial cells (HUVECs) motility, sprouting, and tube formation in vitro in addition to in vivo sprout outgrowth.[99] While OPN is widely distributed in bone matrix helping in bone metabolism, OPN-derived peptide (OPD) does not induce endothelial cell proliferation in vitro. However, like VEGF, it facilitated endothelial cell migration and tube formation using 3D collagen gels [100], suppressed osteoclastogenesis,[91] promoted adhesion and proliferation of MSCs, besides neovascularization in a rat tibial defect model [101]. SPARC113 and SPARC118, two OPN-derived peptides, which exhibit potent angiogenic activity [102], stimulated in vivo angiogenesis when delivered through MMPs degradable hydrogel [103]. TP508 enhanced neoangiogenesis in femoral defects produced in rats [84] and mice [82] following one hour of local administration. The synthetic 12-mer peptides, known as RoY peptides, which were created via the phage-display technology, may also promote in vitro endothelial cell proliferation, tube formation, and sprouting, besides inducing in vivo angiogenesis via a distinct mechanism from VEGF [104].

4. Peptides for Cartilage Regeneration

4.1. Chondroinductive/Chondrogenic Peptides

Numerous peptides have been identified to imitate the functions of ECM components, cell-cell junction molecules, and chondroinductive/chondrogenic ligands triggering specific cell signaling pathways. Motifs derived fibronectin like RGD, decorin, collagen, MMPs have displayed chondrogenic properties. These peptides are often used to functionalize scaffolds encouraging chondrocyte adhesion, migration, and proliferation in addition to MSC differentiation into the chondrogenic lineage.

4.1.1. TGF- β Mimetic Peptides

TGF- β improves cell differentiation, collagen synthesis, and matrix deposition in cartilage tissue engineering.[105] Therefore, peptides mimicking TGF- β activity were used in OC TE for cartilage tissue regeneration. TGF- β mimetic peptides, i.e., cytomodulins (CMs), are oligopeptides containing 4-6 amino acids [106]. CMs immobilized to a solid surface can potentially induce the chondrogenic differentiation compared to its soluble form (Figure 2d). [107,108]

4.1.2. BMP2-Derived/Mimetic Peptides

BMP-2, a member of the TGF- β super-family, is one of the main chondrogenic growth factors that induce in vitro chondrogenic differentiation and cartilage regeneration in vivo. Human MSCs (hMSCs) cultured with ≥ 100 mg/mL of the BMP peptide resulted in glycosaminoglycan (GAGs) production, increased in levels of collagen production and matrix accumulation without extensive upregulation of hypertrophic markers.[107–111] Injection of BMP-2 mimetic CK2.1 peptide into the mice tail vein enhanced chondrogenesis and enhanced articular cartilage formation, without any effects on osteogenesis or BMD.[112] BMP peptide stimulated chondrogenic differentiation of hMSCs without additional growth factors. At a 100 μ g/mL concentration, BMP peptide enhanced proteoglycan production and chondrogenic gene expression without causing hypertrophy, as occurs with BMP-2. [113]

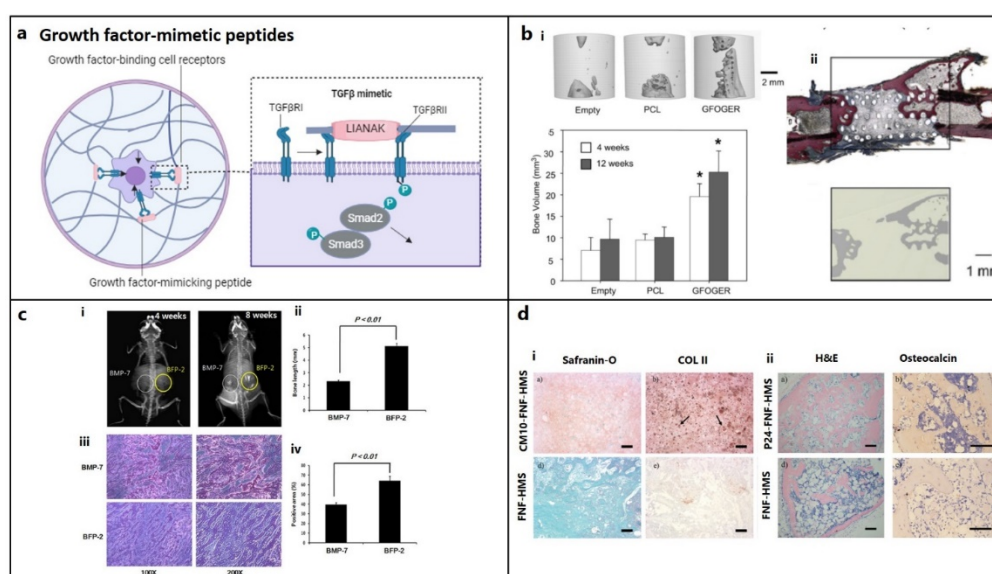


Figure 2. Growth-factor mimetic peptides for bone and cartilage regeneration in osteochondral defects. (a) Growth factor-mimetic peptide epitopes inducing direct signaling, e.g., mimicking transforming growth factor- β (TGF- β) pathway for TGF β receptors (TGF β R) binding. (figure generated via biorender.com) (b) (i) Critical bone defects treated with GFOGER-coated scaffolds shows significantly higher bone formation compared to uncoated PCL scaffolds and empty defect (control), as revealed by micro-CT imaging after 12 weeks of implantation and the plot also depicts a similar pattern at 4 weeks. (ii) Histology confirms that areas of high attenuation in GFOGER-coated sample, as revealed by 2D micro-CT image (inset) are bone tissue (red/pink) (soft tissue appearing blue/green in Sanderson's rapid bone stain).[31] Copyright© 2009 Elsevier Ltd. (c) Bone formation in mice treated with BMP-2 for 4 or 8 weeks in comparison to BMP-7 was evaluated by (i) radiography, (ii) bone length estimation, (iii) histological assessment after hematoxylin and eosin staining and (iv) measurement of the osteogenic area from histology samples using the Image-Pro Plus 6.0 software (n=4).[54] Copyright© 2017, Springer Nature. (d) Histological analysis (i) CM10 conjugated FNF-HMS (CM10-FNF-HMS) with rabbit BMSCs demonstrates positive in SO staining (GAGs) and collagen type II (COL II) staining indicating hyaline cartilage formation after 2 weeks and (ii) P24 conjugated FNF-HMS (P24-FNF-HMS) with rabbit BMSCs reveals significantly higher bone formation in H&E and osteocalcin staining after 5 weeks of subcutaneous implantation, respectively compared to FNF-HMS (D-F) (Scale bars: 100 μ m).[108] Copyright© 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

5. Other supporting Peptides

5.1. Adhesion, Binding, or Affinity Peptides

RGD Peptide: RGD (Arg-Gly-Asp) motif is an essential cell adhesion peptide found in collagen, FN, vitronectin (VN), etc., promotes cell adhesion and/or differentiation through binding with

transmembrane integrin receptors (Figure 3a). RGD sequences, such as GRGDS, RGDS, YRGDS and c(RGDfk), are widely used in the field of cartilage and bone repair. Bone regeneration using cyclic RGD in sheep spinal fusion model was comparable to that of rhBMP-2, due to its increased receptor affinity.[114] RGD, particularly the longer chain RGD (GPenGRGDSPCA), was not always effective in increasing cell adhesion and spreading. This could be because pre-absorbed proteins with stronger binding sites (like FN and VN) compete with weakly adsorbed RGD for cell binding, necessitating covalent attachment. [115,116] RGD is usually capable of increasing cellular adhesion of MSCs, but unable to induce osteogenic differentiation without osteogenic supplements or BMP-2 (Figure 3b). [29,48,49]

PHSRN Peptide: PHSRN (Pro-His-Ser-Arg-Asn) is a FN-derived peptide synergistically enhance cellular activity with RGD and other adhesion peptides through $\alpha 5 \beta 1$ integrin binding, though ineffective alone.[30,117] Due to competitive binding with $\alpha 5 \beta 1$ integrin sites, RGD and PHSRN did not improve the spreading of rat bone MSC on titanium surfaces[118]. However, a dimeric platform consisting of RGD and PHSRN, with a spacing between them resembling natural fibronectin, significantly improved the spreading and proliferation of SAOS-2 osteoblast-like cells when compared to RGD alone or their combination.[117] Further improvements in attachment, spreading, and cell differentiation were made possible by a longer chain RGD that allowed for wider spacings between the peptides like natural fibronectin; nevertheless, such modifications did not result in any osteogenic activity. [119]

FHRRKA and KRSR Peptides: FHRRKA (Phe-His-Arg-Arg-Ile-Lys-Ala) peptide, isolated from heparin binding domain of BSP, significantly enhanced cell proliferation, spreading, as well as matrix mineralization [116,120]. KRSR (Lys-Arg-Ser-Arg) is another peptide isolated from heparin-binding sites of BSP, along with FN, VN, OPN, thrombospondin, etc. [121], increased osteoblast adhesion and osteogenic gene expression. [122–125] A combination of FHRRKA and longer chain RGD (CGNGEPRGDTYRAY) stimulated rat osteoblast matrix mineralization, which was absent when they were employed alone.[94] Similarly, KRSR peptides delivered with RGD promoted cellular attachment on glass surface due to the due to this dual binding mechanism with proteoglycans and integrins, respectively.[121]

N-Cadherin is a calcium-dependent adhesion molecule consisting of five extracellular domains, in which, EC-1 domain having His-Ala-Val (HAV) motif, plays substantial role in cell adhesion. [126] hMSC-seeded nanofibrous hydrogels formed by a cadherin-mimic self-assembling peptide significantly upregulated the expression of chondrogenic markers such Col-II, Sox-9, and aggrecan.[127] hMSCs seeded hydrogels prepared from self-assembling KLD-12 peptide couples with N-cadherin mimetic peptide (HAVDI), remarkably increased chondrogenesis, upregulating cartilage-specific genes expression (collagen II, Aggrecan, and Sox9).[128] hMSC-seeded hyaluronic acid hydrogels functionalized with RGD and N-cadherin mimetic peptide improved osteogenic gene expression, besides new bone formation after 12 weeks of rat MSCs seeded hydrogel implantation into the rat calvarial defects.[129] On the other hand, NEMO-binding domain (NBD) peptide has shown to promote osteoblast differentiation and inhibit bone resorption,[130] osteoclastogenesis [131]. The other integrin binding peptides derived from collagen IV (NYYSNS), fibronectin (KQAGDV, PRARI), laminin (IKLLI, LRGN and SINNNR), fibrinogen (GWTVFQKRLDGS, YSMKKTMMKIIPFNRLTIG and GWTVIQNRQ), netrin-1 (QWRDTWARRLRKFQREKKGKCRKA), CAM-1 (QIDS, LDT, DELPQLVTLPHPNLHGPEILDVPST), thrombospondin (CSVTCG), nidogen-1 (FRGDGQ) have been reported.[132]

Affinity peptides can bind with specific cells, scaffolds, and cytokines associated with cartilage regeneration. Using anti-CD44 antibody, biotin-avidin binding system [133], chondrocyte affinity peptides, [134] E7 peptide, [135], etc., cell adhesion was greatly improved. A TGF- β affinity peptide which can recruit TGF- β to the impaired region [136,137] was ligated to the PA nanofibers, promoted in vitro chondrogenic differentiation of hMSCs and cartilage repair in rabbits. [137] ECM affinity peptides can help mimic the native environment of chondrocytes thus integrated with scaffolds [138,139]. Hydrogels modified with HA - and chondroitin sulfate-binding peptides, significantly promoted BMSCs differentiation into chondrogenic lineage (Figure 3c). [140]

While RGD peptides immobilized at a low density effectively promoted cell adhesion and chondrogenesis [141–143], a higher density of RGD induced hypertrophic transformation of chondrocytes due to the activation of integrin-mediated pathway.[144–146] However, compared to simple RGD adsorption, chemical grafting of RGD peptides on to the biomaterial surface offered improved coating stability and osteoconductivity (Figure 3d). [147] Incorporation of N-cadherin mimetic peptide, HAVDIGGGC, into HA hydrogels increased chondrogenic differentiation at an early stage followed by deposition of cartilaginous matrix [148,149]. Similarly, laminin-related peptide, CDPGYIGSR, significantly promoted cell adhesion with increased ECM deposition by bovine knee chondrocytes seeded on to the polyethylene oxide PEO/chitosan scaffolds.[150]

5.2. Cell Penetrating Peptides (CPPs)

CPPs are peptides derived from bacteria, viruses or synthetic method transverse the cellular membrane to transport their 'cargo' (proteins, siRNA, nanoparticles, oligonucleotides and other peptides), into the cytoplasm. [111]

hMSCs delivered with CPP-conjugated co-activator-associated arginine methyltransferase 1 (CARM1) proteins, transcriptional factor fusion proteins, or recombinant adenovirus expressing BMP-2, promoted in vitro differentiation, and highly mineralized bone formation in vivo. [151–153] NLS-TAT peptides were employed to introduce the hTGF- β 3 plasmid into a self-assembled peptide scaffold or precartilaginous stem cells (PCSCs), and to facilitate chondrogenic differentiation. [154,155]

5.3. Peptides Promoting Cell Migration

For the healing of osteochondral defects, reparative cells, such as fibroblasts, MSCs, osteoblasts, chondrocytes, and endothelial cells, should migrate towards the defect site for participating in various stages of the healing process. ECM proteins and GFs (EGF, PDGF) facilitate cell migration by acting as mitogens or chemotactic factors.[156] Peptides derived from them often exhibit superior cell migration than the parent protein. They work via modulating adhesion proteins (integrins), enzymes (MMPs), kinase-linked receptors, or formyl peptide receptors. SDF-1 is known recruiter of endothelial progenitor cells that differentiate into mature vascular endothelium in the subchondral bone environment, thus promote osteochondral repair.[157] SDF-1 elastin-like peptide (SDF1-ELP) derived from SDF-1 showed comparable in vitro endothelial cell migration and vascularization to SDF, however it was more effective than SDF1 during in vivo healing of full-thickness wounds in diabetic mice. [158] Histatin-1, a 38-mer peptide with antimicrobial properties found in saliva, is a proangiogenic agent that stimulates the adhesion, migration, and angiogenesis of endothelial cells. [159] Other examples are the endogenous histatins, the annexin A1-derived peptide Ac2-26, [160] or the frog-skin derived esculentin 1-21 peptide,[161] induced better wound-healing driven by cell migration. Following administration of the endogenous antimicrobial peptide LL-37, vascularization increased significantly because of enhanced endothelial cell migration. [162] Like FGF-2 (bFGF), FGF-2-mimicking peptide, YRSRKYSSWYVALKR, derived from the 106–120 peptide domain in FGF-2, a partial agonist of FGF receptors, could successfully promote in vitro HUVEC cells proliferation and migration.[163]

5.4. Self-Assembly (SA) Peptides

SA peptides are composed of either alternating hydrophilic and hydrophobic amino acids or peptide amphiphiles (PA), which can self-assemble into β -sheet structures and interwoven nanofibrous hydrogel matrices under physiological conditions [164–166] SA peptides, isolated from various growth factors and bone-related proteins (RANKL-binding peptide, AC-100, B2A) have been studied for osteoblast differentiation and bone regeneration. [53,167,168] RADA16-I (AcN-RADARADARADARADA-CONH₂) peptide immobilized on to the BMP-2 loaded hydrogel promoted osteogenic differentiation of MSCs leading to higher expression of osteogenic-related genes (ALP, OCN, Runx2) and in vivo bone regeneration [169]. PuraMatrix™, a commercially

available RADA16-1 peptide containing hydrogel, strongly supported cartilage formation [170,171]. Repeating units of KLD and RAD in a peptide hydrogel enhanced cartilage formation compared to agarose gel [172].

5.5. Degradable Peptides

Degradable peptides accelerate degradation of scaffolds to facilitate cell penetration and migration, ECM synthesis and deposition, consequently tissue ingrowth. MMPs are the best examples of ECM-degrading proteins. Inclusion of a MMPs-derived peptide (KCGPQGIWGQCK) remarkably promoted GAGs and collagen deposition on to the crosslinked poly (ethylene glycol) norbornene hydrogels.[140,173]

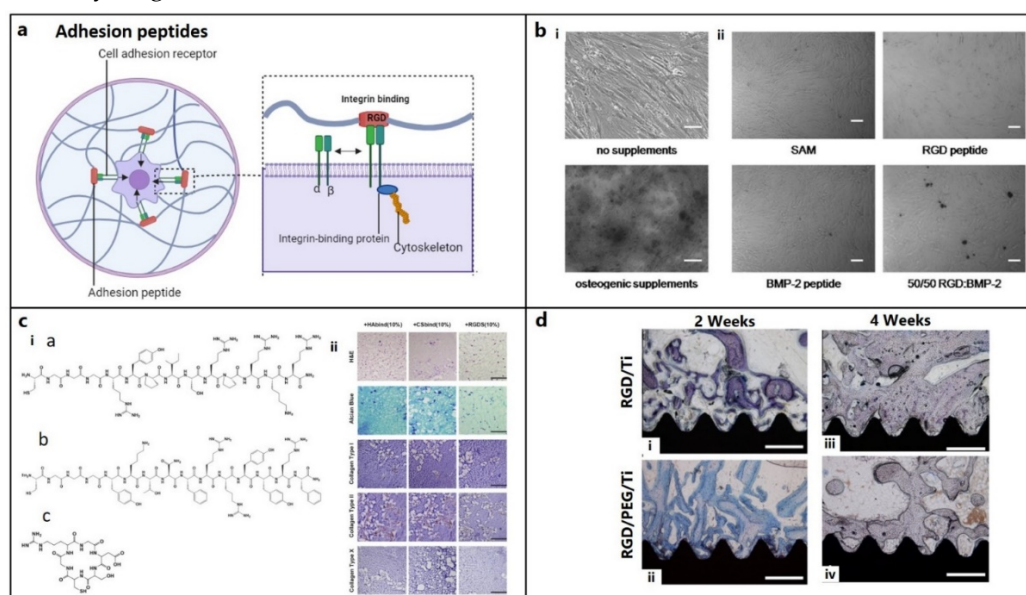


Figure 3. Role of other supporting peptides for osteochondral regeneration. (a) Signaling of the adhesion peptides, e.g., integrin binding. (figure generated via biorender.com) (b) Evaluation of mineralization activity at 3 weeks of hBMSC culture on (i) tissue culture plate with or without osteogenic supplements (ii) self-assembled monolayer (SAM), bone morphogenic protein (BMP) and RGD peptide gradients on glass cover slips supplemented with osteogenic medium. Scale bars 100 μ m.[48] Copyright© 2011 Elsevier Ltd. (i) (c) Structures of acrylated streptococcal collagen-like 2 (Scl2) protein conjugated with hyaluronic acid (HA) binding CGGGYKTNFRRYYRF peptide (HAbind), chondroitin sulfate (CS) binding CGGGYKTNFRRYYRF peptide (CSbind) and cell adhesive GRGDSC peptide (RGDS) (ii) HAbind, CSbind and RGDS peptides based hydrogels cultured with hMSCs for 4 weeks, showed uniform cell and ECM distribution (H&E staining, in panel 1), extensive sGAG accumulation (Alcian Blue staining, in panel 2), high, low, and negative expressions of collagen type I (cartilage marker, in panel 3), type II (bone marker, in panel 4) and type X (hypertrophic marker, in panel 5), respectively (IHC staining), in all hydrogels, indicating chondrogenic differentiation without any hypertrophic transformation. Scale bars: 200 μ m. [140] Copyright© 2015 Elsevier Ltd. (d) Histological analysis showing higher bone formation on RGD/PEG/Ti implants compared to RGD/Ti implants after 2 and 4 weeks of implantation in rabbit femoral condyles. (Mag: 40x; scale bar = 0.5 mm).[147] Copyright© 2011 Elsevier Ltd.

5.6. Antimicrobial and Immunomodulatory Peptides

AMPs or cationic host defense peptides (CHDPs) are oligopeptides (5–100 amino acids), cationic (net charge: +2 to +13), hydrophobic (50% hydrophobic residues), or amphipathic, derived from bacteriophages, bacteria, fungus, plants, and animals, possessing broad-spectrum antibacterial properties without causing antibiotic resistance. [174] Few also have angiogenic, cell migratory, and immunomodulatory properties facilitating tissue regeneration.

A wide range of AMPs have been reported.[175] They include helix-based (LL-37, magainin, melittin), sheet-based (protegrins, bactenecin, defensins) exhibiting β -hairpin like conformation, coil-based (indolicidin, omiganan) which are devoid of both α -helical and β -sheet structures, and composite AMPs, such as melimine (TLISWIKNKRKQRPVSRRRRRRGRRRR), which amalgamates functional regions of mellitin (α -helix) and protamine (random coil with a partially ordered α -helix). LL-37 (LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLPRTES) is a 37-mer peptide α -helical AMP, derived from human cathelicidin antimicrobial protein, possessing antibacterial, antibiofilm, immunomodulation, and angiogenesis properties. Pexiganan (GIGKFLKKAKKFGKAFVKILKK), a synthetic magainin (GIGKFLHSAGKFGKAFVGEIMKS) analogue, PLG0206 (RRWVRRVRRWVRRVVRVRRWVRR) rich in arginine, valine, and tryptophan residues, reduce biofilm formation. Protegrin-1 (RGGRLCYCRRRFCVCVGR), bactenecin (RLCRIVVIRVCR) and its derivatives (RKWRIVVIRVRR and RWRRIVVIRVRR), arginine-rich PEP8R (VRVRVRVRVDPPTVRVRVRV) peptide, show broad-spectrum antimicrobial activities and reduced cytotoxicity. Indolicidin (ILPWKWPWWPWRR), rich in tryptophan and proline, is high potent against bacteria, fungi, and viruses, whereas omiganan (ILRWPWWPWRRK) shows improved bioactivity with reduced cytotoxicity.

AMPs work by disrupting bacterial cell wall or cytoplasmic membrane (Figure 4a), as well as interfering with the other cellular processes like cell wall synthesis. Bactericidal properties of keratin-derived anti-inflammatory KAMP-19 (RAIGGGLSSVGGGSSTIKY) peptide originates from the destruction of bacterial cell membrane via pore formation.[176] α -defensin, known as human Neutrophil Peptide 1 (HNP-1), exhibits high affinity for lipid II, an important component for cell wall synthesis, thereby destabilizes the cell wall integrity [177]. Likewise, RWRWRW-NH₂ delocalizes peripheral membrane proteins in Gram-positive bacteria,[178] LL-37 affects cell wall synthesis by regulating Sfp1 gene, buforin II interrupts cellular functions by interacting with nucleic acids [179], and TO17 degrades DNA and RNA. [180]

Biofilms associated with chronic bone infection are difficult to treat because of bacterial resistance.[181] By interacting with mannan, a key component of cell walls, L-37 decreases cell adhesion before it causes biofilms, therefore lowering Candida infection (Figure 4b).[182] AMP 1037, a 9-mer peptide, decreases swimming and motility of bacteria [183]. Piscidin and sculentin (1–21) degrades pre-formed biofilm matrix by activating nuclease activity and disturbing membrane function, respectively.[184,185]

Anti-inflammatory cytokines (AMPs) can suppress pro-inflammatory cytokines and their associated signaling pathways, or stimulate the synthesis of anti-inflammatory cytokines, which can initiate both an innate and adaptive immune response to eliminate infection and inflammation (Figure 4c). Immunomodulatory metalloproteinases (AMPs) such as cathelicidin-WA stimulate macrophage polarisation from the M1 phenotype (caused by E. Coli) to the M2 phenotype (facilitating bone repair) (Figure 4d).[186] Macrophage polarization plays a significant role in mediating chondrogenesis. Anti-inflammatory M2 macrophages significantly contribute to tissue remodeling and repair, [187] while failure to transform M1 to the M2 subtype induces the progression of cartilage injury.[188]

Regenerative AMPs are beneficial for the regeneration of bone tissue because they can inhibit osteoclastogenesis and stimulate angiogenesis. Histatin-1, 38-mer peptide occurring in saliva, induces angiogenesis and tube formation.[159] On the other hand, human β defensin 3 stimulates MSC osteogenesis,[189] GL13K (GKIILKASLKLL) suppresses osteoclastogenesis,[190] and LL-37 supports the proliferation, migration, and differentiation of MSCs to osteogenic lineage [191].

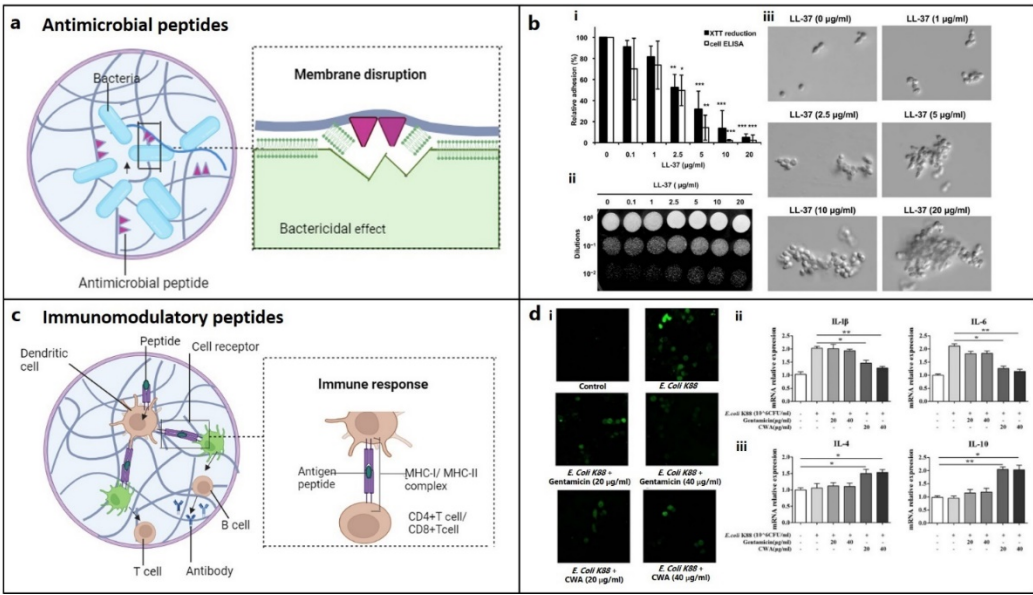


Figure 4. Role of antimicrobial and immunomodulatory peptides for osteochondral regeneration. (a) schematic representation of bacterial cell membrane damage using antimicrobial peptides. (figure generated via biorender.com) (b) Inhibition of *C. albicans* adhesion by different concentrations of LL-37 evaluated by (i) XTT reduction assay and whole-cell ELISA (*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$) (ii) spot assay and (iii) optical microscopy of the floating cells (Mag. 400 $\times$).[182] Copyright© 2011 Tsai et al. (c) mechanism of immunomodulatory peptides eliciting immune-cell response. (figure generated via biorender.com) (d) *E. coli* K88-induced RAW264.7 cells (macrophages) treated with varying doses of cathelicidin-WA (CWA) and gentamicin shows (i) significant reduction of reactive oxygen species (ROS) (in fluorescent images) (ii) decrease in proinflammatory cytokines (IL-1 β , IL-6) and (iii) increase in anti-inflammatory cytokines (IL-4, IL-10) levels.[186] Copyright© 2017 Elsevier B.V.

Table 1. Bioactive peptides for osteochondral regeneration.

Types	Source	Function	Ref
a. Osteogenic peptides			
(i) Osteo-inductive peptides			
GFOGER	Col	$\uparrow$ $\alpha 2\beta 1$ integrin binding, osteoblastic differentiation	[28]
GTPGQGIAGQRGVV (P15 peptide)		$\uparrow$ osteogenic differentiation	[33]
((PKG) ₄ -(POG) ₄ -(DOG) ₄) (KOD peptide)		$\uparrow$ ECM deposition	[37]
DGEA		$\uparrow$ expression of osteogenic markers (ALP, RUNX2, OCN).	[39]
NGLPGPIGP (BCSP TM -1)		$\uparrow$ mineralization	[40]
GPAGPHGPVG, APDPFRMY, TPERYY	BMP-2	$\uparrow$ ALP activity, mineralization, osteogenic gene expression	[41]
KIPKASSVPTELSAISTLYL		$\uparrow$ ALP activity	[42]
SKIPKASSVPTGLSAISTLYL		$\uparrow$ bone formation	[43–45]
AAA (P24)	BMP-2	$\uparrow$ bone formation	[46]
CKIPKPSSVP-TELSAISMPLYL (PEP7)		$\uparrow$ bone formation	[46]

KIPKASSVPTELSAISTLYL		↑ALP activity, osteogenic marker	[47]
NSVNSKIPKACCVPTELSAI, KIPKASSVPTELSAISTLYL, DWIVA		↑Osteogenic differentiation, in vivo bone formation	[12]
RKKNPNCRRH	BMP-4	↑Osteogenic differentiation	[55]
VEHDKEFFHPRYHH (BFP-2)		↑Osteogenic differentiation	[54]
TVPKPSSAPTQLNAISTLYF, GQGFSPYKAVFSTQ, ETLDGQSINPKLAGL	BMP-7	↑Osteogenic differentiation	[55]
KVGKACCVPTKLSPISVLY	BMP-9	↑Osteogenic differentiation	[55]
CK2.2, CK2.3	synthetic	↑ BMP signaling	[57]
PTHrP1–34, PTHrP1–36, PTHrP107–111	PTH	↑ Osteoblast differentiation, bone formation	[64–66]
CGRP- α and β -CGRP	CGRP	↑ Osteogenic differentiation, bone formation	[67–70]
ALKRQGRTLYGFGG (OGP)	Mammalian blood	↑ Osteogenic differentiation, ALP, OCN and collagen secretion, mineralization	[76–78]
AGYKPDEGKRGDACEGDS GGPFV (TP508)	Thrombin	↑ chemotaxis, proliferation, osteogenic differentiation	[79,80]
FN III9-10/12-14	FN	↑ osteoblast activity, mineralization	[85]
CBM	OPN	↑ osteogenic differentiation, bone formation	[90]
SVVYGLR	OPN	↑ osteogenesis, neovascularization	[91–93]
FHRRIKA	BSP	↑ osteoblast activity, mineralization	[94]
(ii) Angiogenic peptides			
QK	VEGF	↑EC migration, proliferation	[97]
PBA2-1c	PDGF-BB	Blood vessels formation	[98]
Exendin-4	Exendin-4	↑ tube formation of HUVECs	[99]
SPARC113, SPARC118	OPN	↑ in vivo angiogenesis	[103]
TP508	Thrombin	↑ neo-angiogenesis	[84]
RoY	Synthetic	↑ EC proliferation, sprouting, in vivo angiogenesis	[104]
b. Chondroinductive peptides			
CMs	TGF- β	↑Chondrogenic differentiation	[107,108]
CK2.1	synthetic	↑Chondrogenesis	[112]
c. Other supporting peptides			
(i) Adhesion, binding, affinity peptides			
RGD	Col, FN, VN	↑Cellular adhesion/ or differentiation	[114]
PHSRN	FN	↑Cell adhesion	[30,117]

FHRRIKA	BSP	↑Cell proliferation, spreading, mineralization	[116,120]
KRSR	BSP, FN, VN, OPN, thrombospondin	↑Osteoblast adhesion, osteogenic gene expression	[122–125]
HAV	N-Cadherin	↑Cell adhesion	[126]
NEMO-binding domain (NBD) peptide	synthetic	↑Osteoblast differentiation ↓bone resorption, osteoclastogenesis	[130] [131]
CDPGYIGSR	Laminin	↑Cell adhesion, ECM deposition	[150]
(ii) Peptides supporting cell migration			
SDF1-ELP	SDF-1	EC migration, vascularization	[158]
Histatin-1	Saliva	EC adhesion, migration, angiogenesis	[159]
Ac2-26	Annexin A1	Cell migration	[160]
Esculentin 1-21	Frog-skin	Cell migration	[161]
LL-37	Human	EC migration	[162]
(ii) Cell penetrating peptides (CPPs)			
NLS-TAT	HIV-1 Tat protein	↑Chondrogenic differentiation	[154,155]
(iii) Self-assembly (SA) peptides			
AcN-RADARADARADA-CONH ₂ (RADA16-I)	synthetic	↑ ALP, OCN, Runx2	[169]
(iv) Degradable peptides			
KCGPQGIWGQCK	MMP-derived	↑GAGs, collagen deposition	[140,173]
Antimicrobial and immunomodulatory peptides			
TLISWIKNKRKQRPVSRRR RRRGRRRR (Melamine)	synthetic	destabilization of cell membrane	[175]
LLGDFFRKSKEKIGKEFKRIV QRIKDFLRNLPVPRTE (LL-37)	human cathelicidin	inhibit cell wall synthesis	[179]
GIGKFLKKAKKFGKAFVKIL KK (Pexiganan)	synthetic analogue of magainin2	disrupts membrane	[175]
GIGKFLHSAGKFGKAFVGEI MKS (Magainin-1)	frog skin	destabilizes or disrupts bacterial membrane	[175]
RRWVRRVRRWVRRVVRVV RRWVRR (PLG0206)	synthetic	disrupts cell membrane	[175]
RGGRLCYCRRRFCVCVGR (Protegrin-1)	porcine leukocytes	disrupts cell membrane	[175]
RLCRIVVIRVCR (Bactenecin)	bovine neutrophils	inhibit protein synthesis	[175]
VRVRVRVRVDPPTRVVRV RV (PEP8R)	synthetic	disrupts bacterial cell membrane	[175]
ILPWKWPWWPWRR (Indolicidin)	bovine neutrophil	Increase cell membrane permeability	[175]
ILRWPWWPWRRK (Omiganan)	synthetic	destabilizes cell membrane	[175]

RAIGGGLSSVGGGSSTIKY (KAMP-19)	keratin	pore formation in bacterial cell membra	[176]
HNP-1	human neutrophil	destabilizes cell wall integrity	[177]
RWRWRW-NH ₂	synthetic	delocalizes peripheral membrane proteins	[178]
AMP 1037	synthetic	↓swimming and motility of bacteria, gene expression	[183]
Piscidin and sculentin 1–21	fish	degrades biofilm	[184,185]
Histatin-1, 38	saliva	antimicrobial	[159]
β defensin 3	human	immunomodulator	[189]
GKIIKLKASLKLL (GL13K)	salivary protein	delocalizes cell membrane lipids	[190]

Abbreviations: BMP: Bone morphogenic protein, ALP: Alkaline Phosphatase, OCN: Osteocalcin, Col: Collagen, CK: Calmodulin Complexes, PTH: Parathyroid hormone, CGRP: Calcitonin gene-related peptide, OGP: Osteogenic growth peptide, FN: Fibronectin, VN: Vironectin, OPN: Osteopontin, CBM: Collagen-binding motif, BSP: bone sialoprotein, VEGF: Vascular endothelial growth factor, PDGF-BB, EC: Endothelial cell; CMs: Cytomodulins, GAG: Glycosaminoglycan; SDF-1: Stromal cell-derived factor 1, SDF1-ELP: SDF1 elastin-like peptide, CK2: casein kinase II

6. Peptide-Conjugated Biomaterials

Natural ECM-mimetic biomaterials like collagen, gelatin, chitosan, alginate, and silk, etc., are often combined with synthetic materials, such as polyethylene glycol (PEG), polylactic acid (PLA), and polycaprolactone (PCL), to fabricate an OC construct possessing tailorable strength, bioactivity, biocompatibility, and biodegradation characteristics, with reduced hydrophobicity, immunogenicity, and inflammatory properties. Bioactive materials, such as hydroxyapatite, calcium phosphate, and biological ceramics, are also combined to encourage biomineralization.[22]

6.1. Osteo-Inductive Scaffold

Delivery of BMP2-derived KIPKASSVPTELSAISTLYL peptide through TCP scaffolds promoted bone healing rabbit radial bone-defect.[192] BMP-2 mimetic peptides attached to a substrate enhanced BMSC attachment and differentiation without affecting mineralization. [49] However, when these peptides were combined with RGD, the rate of mineralization increased because RGD induced higher interaction cells in absence of osteogenic supplementation. [48] Incorporation of BMP-2-mimetic peptide conjugated to a heptaglutamate moiety (E7-BMP-2) into the mineralized PLGA-collagen-gelatin nanofiber promoted bone formation in critical-sized alveolar bone defects in rats after 4 weeks of implantation.[193] Electrospun porous cellulose acetate nanofibrous mat modified with adhesive peptides KRSR, RGD, and growth factor BMP-2 enhanced adhesion and proliferation of pre-osteoblastic cells.[194] PCL nanofibrous scaffolds containing different concentrations of the bioactive with KIPKASSVPTELSAISTLYL peptide derived from the BMP-2 developed by Lukasova et al. Scaffolds seeded with porcine MSCs showed increased expression of OCN and collagen I significantly osteogenic differentiation.[195] KRSR, BMP mimetic peptides, and FHRIKKA were successfully integrated into the outer, middle, and inner layers of PLGA electrospun membranes through layer-by-layer assembly, and such modification demonstrated synergistic effects on bone healing by enhancing cell attachment, differentiation, and mineralization. [196] FHRIKKA and KRSR peptides covalently linked with the surface of polymeric nanoparticles significantly improved MSC attachment and ALP activity due to an osteogenic differentiation, which was not very profound in case of KRSR.[197,198] Immobilization of KRSR on a silane functionalized borosilicate glass,[121] or micropatterning with KRSR on borosilicate glass,[199] and the other

substrates.[116,124,125,200] selectively enhanced osteoblasts adhesion through $\alpha\text{v}\beta 5$ integrin receptors binding.

On the other hand, GFOGER functionalized PEG-BMP-2 hydrogels increased in vitro cell spreading and differentiation of BMSCs into osteogenic lineage, besides improved bone healing in mice radial defect model even in absence of BMP-2.[29] Implants coated with GFOGER were found to improve peri-implant bone regeneration and osseointegration[201]. However, hydroxyapatite disks adsorbed with GFOGER failed to attach cells with a decrease in cell spreading,[115] possibly due to a lack in nature-mimicking conformation of GFOGER.[31] P15-coated bovine bone grafts allowed faster recovery of periodontal defects in humans. [202] P-15-containing bone graft substitutes could facilitate the process of early bone formation[203,204], bone healing and regeneration[205]. P24 delivery to the defect site was achieved by encapsulating in chitosan microspheres,[50] covalent binding with polymeric backbone, [43] or simple adsorption on hydroxyapatite,[43] greatly enhancing the bioactive properties of the scaffolds.

DGEA immobilized on HA was found to enhance the adhesion and osteoblastic differentiation of MSCs, and new bone formation[206]. BCSPTM-1, when delivered through HA and tricalcium phosphate (TCP) grafts, stimulated ALP activity in murine calvarial osteoprogenitor cells[207]. OGP rich PLGA scaffold accelerated bone healing in 1.5-cm rabbit segmental defects.[208] PEG hydrogel containing PTH1–34 promoted in situ bone augmentation in rabbits, [209] whereas TP508 loaded PPF composite and microsphere scaffolds showed enhanced bone formation in rabbit segmental bone defects. [210] RGD coated implants were found to have an increased peri-implant bone formation and enhanced direct bone apposition even in areas of poor surrounding bone. [147,211–213] An increased osteoblast density was observed, when anodized nanotubular titanium surface was coated with RGD or RGDS (Arg-Gly-Asp-Ser).[214,215]

6.2. Chondro-Inductive Scaffolds

Collagen type II-derived peptide conjugated zwitterionic carbon nano-dots (pCD) induced chondrogenic differentiation of ADMSCs. Pluronic F-127 hydrogel mediated delivery of pCD could successfully promote rabbit auricular cartilage defect healing after 60 days.[179] Self-assembled KLD12 and KLD12-CMP7 peptide hydrogels loaded into poly (L-lactide-co-caprolactone) scaffolds could successfully create a chondrogenic microenvironment to rat BMSCs seeded scaffolds after subcutaneous implantation in nude mice.[216] Self-assembling PA scaffolds loaded with a TGF-binding domain, HSNGLPLGGGSEEEAAVVV(K)-CO(CH₂)₁₀CH₃ could support viability and chondrogenic differentiation of hMSC, besides accelerated healing of articular cartilage defects in rabbit.[137] Similarly, HSNGLPL peptide coated porous chitosan scaffolds or gelatin methacryloyl (GelMA) hydrogel successfully induced chondrogenic differentiation of MSCs and recovery of osteochondral defects in mice and rabbit model.[217,218] RGD coating on the synthetic bioinert materials surface significantly improved properties like cell adhesion, viability, and differentiation. Composite scaffolds were prepared from RGD functionalized hydroxyapatite/methoxy poly (ethylene glycol)-block-poly(ϵ -caprolactone) (1:2 ratio) scaffold followed by infiltration of TGF- β 1 functionalized glycidyl methacrylate-hyaluronic acid hydrogel. The scaffolds significantly upregulated the expression of cartilage-specific genes (aggrecan, Col2a1, Sox9) with higher accumulation of sulphated glycosaminoglycan (sGAG), whereas successful OC defect healing was also achieved after 12 weeks of implantation in rabbit knee defect model.[219]

6.3. Multifunctional Scaffolds

Subcutaneous injection of nanofibrous hollow microspheres conjugated with TGF- β 1 mimetic CM10 combined with rabbit BMSCs successfully induced ectopic cartilage formation in nude mice via chondrogenic differentiation of MSCs; in contrast, BMP-2 mimetic P24 peptide-loaded microspheres demonstrated osteogenic activity leading to bone formation.[108] Implantation of 3D printed porous bi-layered scaffolds infiltrated with TGF- β 1 binding HSNGLPLGG(MA) peptides-rich GelMA hydrogels in the top layer and hydroxyapatite in the bottom layer successfully repaired the osteochondral of defects in SD rats through simultaneous cartilage and bone regeneration,

respectively.[220] Hyaluronic-acid-based hydrogel particles (HGP) functionalized with cysteine-tagged CK2.1 peptide showed promising results for cartilage repair in a mouse model, without inducing chondrocyte hypertrophy, unlike BMP-2. [57] Whereas, using same model, CK2.2 and CK2.3 peptides induced osteoblast differentiation and mineralization, similar to BMP-2 [112]. RGD functionalized poly (ethylene glycol)-diacrylate (PEGDA) hydrogel encapsulating rat osteoblasts facilitated the adhesion and spreading of rat osteoblasts leading to matrix mineralization.[221] RGD immobilized on hydroxyapatite improved healing of femoral condylar defects in rabbits.[222] Though a longer chain RGD, was unable to do the same without an TGF- β supplementation.[223] RGD peptide attached to glass coverslips through silanization, did not show osteoblast adhesion, since attachment happens through integrin binding.[121]

Wang et al developed cryogenic 3D printed bilayer β -tricalcium phosphate/PLGA osteochondral scaffold, enriched with osteogenic peptide sequence, KIPKA SSVPT ELSAI STLYL SGGC, and TGF- β 1 loaded collagen I hydrogel for cartilage repair. The osteochondral scaffold showed improved chondrogenic differentiation of rBMSCs, by up-regulated expression of chondrogenic markers and glycosaminoglycan (GAG) production, while enhanced osteogenic differentiation of rBMSCs at the subchondral layer by up-regulated expression RUNX2, osteocalcin and alkaline phosphatase (ALP), and calcium deposition.[224]

Due to the bactericidal or anti-biofilm, immunomodulatory, and regenerative capacity, AMPs with adequate cytocompatibility have been explored for bone and cartilage tissue regeneration. Titanium surface immobilized with Mel4 peptides demonstrated significant antimicrobial efficacy after implantation into the rabbit femoral defects.[225] While GL13K peptide (GKIIKLKASLKLL-NH₂) coated titanium surface could effectively inhibit peri-implantitis through immunomodulatory function[226,227] Titanium plate modified with antimicrobial LF1-11-coupled RGD peptide demonstrated good antibacterial properties with improved osteoblast adhesion, proliferation and mineralization.[228] Inclusion of HHC-36 (KRWWKWWRR), a broad-spectrum cationic AMP, and osteoconductive Laponite nanosilicates into GelMA hydrogel, which was used for coating of titanium implant surface significantly promoted expression of osteogenic-related genes and mineralization of hMSCs, besides effective inhibition of Gram-positive bacteria (*S. aureus* and *S. epidermidis*) and Gram-negative bacteria (*P. aeruginosa* and *E. coli*).[229] On the other hand, HA bone scaffolds coated with PSI10 (RRWPWWPWRR) and BMP2-MP [230] or a nano-hydroxyapatite coated titanium surface containing antimicrobial human β -defensin 3 (HBD-3) peptide and BMP-2,[231] significantly promoted antibacterial and osteogenic activity of the scaffolds.

Multifunctional PEEK coated with lithium-ion and mussel-inspired antimicrobial peptide enhanced osteogenesis-associated genes/proteins expression, and osseointegration at bone-implant interface, besides inhibition of *E. coli* and *S. aureus*. [232] Coated with mouse beta-defensin-14 (MBD-14) also improved antimicrobial and osseointegration properties of PEEK.[233] KR-12 analogue immobilized on the surface of titanium or PEEK bone implants via a polydopamine coating showed remarkable antibacterial activity, osteogenic differentiation of MSCs and peri-implant bone formation.[234,235]

7. Summary and Outlook

The goal of bioengineering is tissue emulation, including mimicking ECM and facilitating cell-material interaction, as well as tissue shape, function, and the in vivo milieu. Peptides, as the cell-instructive molecular building blocks, can bind or co-assemble with ECM or synthetic biomaterials, that not only offer structural and functional complexity, but also additively or synergistically work for better cellular activity, immune response, or tissue remodeling. A significant number of peptides were investigated as potential candidates for the promoting bone and cartilage healing, either directly by promoting cell adhesion, migration, angiogenesis, and differentiation into osteo/chondrogenic lineage, or indirectly by helping cargo penetration into the cells. Considering the structural and functional heterogeneity of an osteochondral unit, a strategy combining multiple peptides with biomaterials for simultaneous bone and cartilage tissue regeneration has been proposed. For example, a collagen-mimetic GFOGER or P15 peptide, or a BMP-2 mimetic P24 or BFP-2 peptide can

be combined with VEGF mimetic QK peptides or TP508 or synthetic RoY peptides for osteo-inductive effect. On the other hand, a TGF- β or BMP-2 mimetic peptide can be used to induce chondrogenic activity in conjunction with RGD or PHSRN conjugated hydrogel for improved adhesion and proliferation, or SDF1-ELP or MMP-cleavable peptide-based hydrogels for cell migration into the hydrogel matrix. Hydrogel nanocomposites with improved mechanical strength and biological properties may be created by co-assembling peptides with structural proteins or inorganic fillers or by short SA peptides with macromolecules. Peptides that prevent microbial infection or help pro-inflammatory M1 to anti-inflammatory M2 macrophage polarization can be added to overcome post-implantation issues. The advent of electrospinning, inkjet printing, bioprinting, and other advanced manufacturing strategies enable fabrication of peptide hydrogel constructs with complex geometry and multi-scale hierarchy resembling native tissue. More focus should be given on investigating phage display or artificial intelligence (AI) and machine learning (ML) tools, which can provide a pattern-based search to find novel sequences or bioactive motifs from full-length proteins by establishing rules for protein interactions and signaling.

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Reference

1. Yildirim, N.; Amanzhanova, A.; Kulzhanova, G.; Mukasheva, F.; Eriskin, C. Osteochondral interface: regenerative engineering and challenges. *ACS Biomaterials Science & Engineering* **2023**, *9*, 1205-1223.
2. Steinmetz, J.D.; Culbreth, G.T.; Haile, L.M.; Rafferty, Q.; Lo, J.; Fukutaki, K.G.; Cruz, J.A.; Smith, A.E.; Vollset, S.E.; Brooks, P.M. Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet Rheumatology* **2023**, *5*, e508-e522.
3. Howell, M.; Liao, Q.; Gee, C.W. Surgical management of osteochondral defects of the knee: an educational review. *Current Reviews in Musculoskeletal Medicine* **2021**, *14*, 60-66.
4. Zhu, M.; Zhong, W.; Cao, W.; Zhang, Q.; Wu, G. Chondroinductive/chondroconductive peptides and their-functionalized biomaterials for cartilage tissue engineering. *Bioactive materials* **2022**, *9*, 221-238.
5. Madry, H. Surgical therapy in osteoarthritis. *Osteoarthritis and cartilage* **2022**, *30*, 1019-1034.
6. Wei, W.; Dai, H. Articular cartilage and osteochondral tissue engineering techniques: Recent advances and challenges. *Bioactive materials* **2021**, *6*, 4830-4855.
7. Makris, E.A.; Gomoll, A.H.; Malizos, K.N.; Hu, J.C.; Athanasiou, K.A. Repair and tissue engineering techniques for articular cartilage. *Nature Reviews Rheumatology* **2015**, *11*, 21-34.
8. Chen, L.; Wei, L.; Su, X.; Qin, L.; Xu, Z.; Huang, X.; Chen, H.; Hu, N. Preparation and Characterization of Biomimetic Functional Scaffold with Gradient Structure for Osteochondral Defect Repair. *Bioengineering* **2023**, *10*, 213.
9. Rizzo, M.G.; Palermo, N.; D'Amora, U.; Oddo, S.; Guglielmino, S.P.P.; Conoci, S.; Szychlinska, M.A.; Calabrese, G. Multipotential Role of Growth Factor Mimetic Peptides for Osteochondral Tissue Engineering. *International Journal of Molecular Sciences* **2022**, *23*, 7388.
10. Gonçalves, A.M.; Moreira, A.; Weber, A.; Williams, G.R.; Costa, P.F. Osteochondral tissue engineering: The potential of electrospinning and additive manufacturing. *Pharmaceutics* **2021**, *13*, 983.
11. Bullock, G.; Atkinson, J.; Gentile, P.; Hatton, P.; Miller, C. Osteogenic peptides and attachment methods determine tissue regeneration in modified bone graft substitutes. *Journal of Functional Biomaterials* **2021**, *12*, 22.
12. Visser, R.; Rico-Llanos, G.A.; Pulkkinen, H.; Becerra, J. Peptides for bone tissue engineering. *Journal of controlled release* **2016**, *244*, 122-135.
13. Pountos, I.; Panteli, M.; Lampropoulos, A.; Jones, E.; Calori, G.M.; Giannoudis, P.V. The role of peptides in bone healing and regeneration: a systematic review. *BMC medicine* **2016**, *14*, 1-15.
14. Ai, C.; Lee, Y.H.D.; Tan, X.H.; Tan, S.H.S.; Hui, J.H.P.; Goh, J.C.-H. Osteochondral tissue engineering: perspectives for clinical application and preclinical development. *Journal of Orthopaedic Translation* **2021**, *30*, 93-102.
15. Wang, Z.; Le, H.; Wang, Y.; Liu, H.; Li, Z.; Yang, X.; Wang, C.; Ding, J.; Chen, X. Instructive cartilage regeneration modalities with advanced therapeutic implantations under abnormal conditions. *Bioactive Materials* **2022**, *11*, 317-338.

16. Bittner, S.M.; Guo, J.L.; Melchiorri, A.; Mikos, A.G. Three-dimensional printing of multilayered tissue engineering scaffolds. *Materials Today* **2018**, *21*, 861-874.
17. Kapat, K.; Rameshbabu, A.P.; Maity, P.P.; Mandal, A.; Bankoti, K.; Dutta, J.; Das, D.K.; Dey, G.; Mandal, M.; Dhara, S. Osteochondral defects healing using extracellular matrix mimetic phosphate/sulfate decorated GAGs-agarose gel and quantitative micro-CT evaluation. *ACS Biomaterials Science & Engineering* **2018**, *5*, 149-164.
18. Bittner, S.M.; Guo, J.L.; Mikos, A.G. Spatiotemporal control of growth factors in three-dimensional printed scaffolds. *Bioprinting* **2018**, *12*, e00032.
19. Gibson, J.D.; O'Sullivan, M.B.; Alaei, F.; Paglia, D.N.; Yoshida, R.; Guzzo, R.M.; Drissi, H. Regeneration of articular cartilage by human ESC-derived mesenchymal progenitors treated sequentially with BMP-2 and Wnt5a. *Stem cells translational medicine* **2017**, *6*, 40-50.
20. McGee-Lawrence, M.E.; Carpio, L.R.; Bradley, E.W.; Dudakovic, A.; Lian, J.B.; van Wijnen, A.J.; Kakar, S.; Hsu, W.; Westendorf, J.J. Runx2 is required for early stages of endochondral bone formation but delays final stages of bone repair in Axin2-deficient mice. *Bone* **2014**, *66*, 277-286.
21. Du, X.; Xie, Y.; Xian, C.J.; Chen, L. Role of FGFs/FGFRs in skeletal development and bone regeneration. *Journal of cellular physiology* **2012**, *227*, 3731-3743.
22. Guo, J.L.; Diaz-Gomez, L.; Xie, V.Y.; Bittner, S.M.; Jiang, E.Y.; Wang, B.; Mikos, A.G. Three-dimensional printing of click functionalized, peptide patterned scaffolds for osteochondral tissue engineering. *Bioprinting* **2021**, *22*, e00136.
23. Einhorn, T.A.; Gerstenfeld, L.C. Fracture healing: mechanisms and interventions. *Nature Reviews Rheumatology* **2015**, *11*, 45-54.
24. Pozos-Guillén, A.; Molina, G.; Soviero, V.; Arthur, R.A.; Chavarria-Bolaños, D.; Acevedo, A.M. Management of dental caries lesions in Latin American and Caribbean countries. *Brazilian Oral Research* **2021**, *35*, e055.
25. Mehta, M.; Schmidt-Bleek, K.; Duda, G.N.; Mooney, D.J. Biomaterial delivery of morphogens to mimic the natural healing cascade in bone. *Advanced drug delivery reviews* **2012**, *64*, 1257-1276.
26. Gerber, H.-P.; Vu, T.H.; Ryan, A.M.; Kowalski, J.; Werb, Z.; Ferrara, N. VEGF couples hypertrophic cartilage remodeling, ossification and angiogenesis during endochondral bone formation. *Nature medicine* **1999**, *5*, 623-628.
27. Calori, G.; Alibisetti, W.; Agus, A.; Iori, S.; Tagliabue, L. Risk factors contributing to fracture non-unions. *Injury* **2007**, *38*, S11-S18.
28. Reyes, C.D.; Petrie, T.A.; Burns, K.L.; Schwartz, Z.; García, A.J. Biomolecular surface coating to enhance orthopaedic tissue healing and integration. *Biomaterials* **2007**, *28*, 3228-3235.
29. Shekaran, A.; García, J.R.; Clark, A.Y.; Kavanaugh, T.E.; Lin, A.S.; Guldborg, R.E.; García, A.J. Bone regeneration using an alpha 2 beta 1 integrin-specific hydrogel as a BMP-2 delivery vehicle. *Biomaterials* **2014**, *35*, 5453-5461.
30. Connelly, J.; Petrie, T.; García, A.; Levenston, M. Fibronectin-and Collagen-Mimetic Ligands Regulate BMSC Chondrogenesis in 3D Hydrogels. *European cells & materials* **2011**, *22*, 168.
31. Wojtowicz, A.M.; Shekaran, A.; Oest, M.E.; Dupont, K.M.; Templeman, K.L.; Huttmacher, D.W.; Guldborg, R.E.; García, A.J. Coating of biomaterial scaffolds with the collagen-mimetic peptide GFOGER for bone defect repair. *Biomaterials* **2010**, *31*, 2574-2582.
32. Kolambkar, Y.M.; Bajin, M.; Wojtowicz, A.; Huttmacher, D.W.; García, A.J.; Guldborg, R.E. Nanofiber orientation and surface functionalization modulate human mesenchymal stem cell behavior in vitro. *Tissue Engineering Part A* **2014**, *20*, 398-409.
33. Bhatnagar, R.S.; Qian, J.J.; Wedrychowska, A.; Sadeghi, M.; Wu, Y.M.; Smith, N. Design of biomimetic habitats for tissue engineering with P-15, a synthetic peptide analogue of collagen. *Tissue Engineering* **1999**, *5*, 53-65.
34. Hestehave Pedersen, R.; Rasmussen, M.; Overgaard, S.; Ding, M. Effects of P-15 peptide coated hydroxyapatite on Tibial defect repair in vivo in Normal and osteoporotic rats. *BioMed Research International* **2015**, *2015*.
35. Schmitt, C.M.; Koepple, M.; Moest, T.; Neumann, K.; Weisel, T.; Schlegel, K.A. In vivo evaluation of biofunctionalized implant surfaces with a synthetic peptide (P-15) and its impact on osseointegration. A preclinical animal study. *Clinical Oral Implants Research* **2016**, *27*, 1339-1348.
36. Kumar, V.A.; Taylor, N.L.; Jalan, A.A.; Hwang, L.K.; Wang, B.K.; Hartgerink, J.D. A nanostructured synthetic collagen mimic for hemostasis. *Biomacromolecules* **2014**, *15*, 1484-1490.
37. Uysal, O.; Arslan, E.; Gulseren, G.; Kilinc, M.C.; Dogan, I.; Ozalp, H.; Caglar, Y.S.; Guler, M.O.; Tekinay, A.B. Collagen peptide presenting nanofibrous scaffold for intervertebral disc regeneration. *ACS Applied Bio Materials* **2019**, *2*, 1686-1695.

38. Harbers, G.M.; Healy, K.E. The effect of ligand type and density on osteoblast adhesion, proliferation, and matrix mineralization. *Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials* **2005**, *75*, 855-869.
39. Anderson, J.M.; Vines, J.B.; Patterson, J.L.; Chen, H.; Javed, A.; Jun, H.-W. Osteogenic differentiation of human mesenchymal stem cells synergistically enhanced by biomimetic peptide amphiphiles combined with conditioned medium. *Acta biomaterialia* **2011**, *7*, 675-682.
40. Sindrey, D.; Pugh, S.; Smith, T. Connective Tissue Stimulating Peptides. US20050288229A1, US Patent 2005/0288229 A1 (2005).
41. Huang, W.; Yu, K.; Kang, M.; Wang, Q.; Liao, W.; Liang, P.; Liu, G.; Cao, Y.; Miao, J. Identification and functional analysis of three novel osteogenic peptides isolated from tilapia scale collagen hydrolysate. *Food Research International* **2022**, *162*, 111993.
42. Lam, H.; Li, S.; Lou, N.; Chu, J.; Bhatnagar, R. Synthetic peptides cytomodulin-1 (CM-1) and cytomodulin-2 (CM-2) promote collagen synthesis and wound healing in vitro. In Proceedings of the The 26th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2004; pp. 5028-5030.
43. Lin, Z.-Y.; Duan, Z.-X.; Guo, X.-D.; Li, J.-F.; Lu, H.-W.; Zheng, Q.-X.; Quan, D.-P.; Yang, S.-H. Bone induction by biomimetic PLGA-(PEG-ASP) n copolymer loaded with a novel synthetic BMP-2-related peptide in vitro and in vivo. *Journal of Controlled Release* **2010**, *144*, 190-195.
44. Duan, Z.; Zheng, Q.; Guo, X.; Yuan, Q.; Chen, S. Experimental research on ectopic osteogenesis of BMP2-derived peptide P24 combined with PLGA copolymers. *Journal of Huazhong University of Science and Technology* **2007**, *27*, 179-182.
45. Saito, A.; Suzuki, Y.; Ogata, S.I.; Ohtsuki, C.; Tanihara, M. Prolonged ectopic calcification induced by BMP-2-derived synthetic peptide. *Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials* **2004**, *70*, 115-121.
46. Kang, E.-J.; Kim, S.-K.; Eom, T.-G.; Choi, K.-O.; Lee, T.-H. Evaluation of the osteogenic activity of the BMP-2 mimetic peptide, PEP7, in vitro and in vivo. *International Journal of Oral & Maxillofacial Implants* **2013**, *28*.
47. Saito, A.; Suzuki, Y.; Ogata, S.-i.; Ohtsuki, C.; Tanihara, M. Activation of osteo-progenitor cells by a novel synthetic peptide derived from the bone morphogenetic protein-2 knuckle epitope. *Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics* **2003**, *1651*, 60-67.
48. Moore, N.M.; Lin, N.J.; Gallant, N.D.; Becker, M.L. Synergistic enhancement of human bone marrow stromal cell proliferation and osteogenic differentiation on BMP-2-derived and RGD peptide concentration gradients. *Acta biomaterialia* **2011**, *7*, 2091-2100.
49. He, X.; Ma, J.; Jabbari, E. Effect of grafting RGD and BMP-2 protein-derived peptides to a hydrogel substrate on osteogenic differentiation of marrow stromal cells. *Langmuir* **2008**, *24*, 12508-12516.
50. Niu, X.; Feng, Q.; Wang, M.; Guo, X.; Zheng, Q. Porous nano-HA/collagen/PLLA scaffold containing chitosan microspheres for controlled delivery of synthetic peptide derived from BMP-2. *Journal of Controlled Release* **2009**, *134*, 111-117.
51. Cho, Y.-J.; Yeo, S.-I.; Park, J.-W.; Shin, H.-I.; Bae, Y.-C.; Suh, J.-Y. The effects of synthetic peptide derived from hBMP-2 on bone formation in rabbit calvarial defect. *Tissue Eng Regen Me* **2008**, *5*, 488-497.
52. Lee, J.S.; Lee, J.S.; Murphy, W.L. Modular peptides promote human mesenchymal stem cell differentiation on biomaterial surfaces. *Acta biomaterialia* **2010**, *6*, 21-28.
53. Saito, A.; Suzuki, Y.; Kitamura, M.; Ogata, S.I.; Yoshihara, Y.; Masuda, S.; Ohtsuki, C.; Tanihara, M. Repair of 20-mm long rabbit radial bone defects using BMP-derived peptide combined with an α -tricalcium phosphate scaffold. *Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials* **2006**, *77*, 700-706.
54. Kim, H.K.; Lee, J.S.; Kim, J.H.; Seon, J.K.; Park, K.S.; Jeong, M.H.; Yoon, T.R. Bone-forming peptide-2 derived from BMP-7 enhances osteoblast differentiation from multipotent bone marrow stromal cells and bone formation. *Experimental & molecular medicine* **2017**, *49*, e328-e328.
55. Patterson, J. Peptide-functionalized Biomaterials with Osteoinductive or Anti-biofilm Activity. *Racing for the Surface: Antimicrobial and Interface Tissue Engineering* **2020**, 129-168.
56. Bragdon, B.; Thinakaran, S.; Moseychuk, O.; Gurski, L.; Bonor, J.; Price, C.; Wang, L.; Beamer, W.G.; Nohe, A. Casein kinase 2 regulates in vivo bone formation through its interaction with bone morphogenetic protein receptor type Ia. *Bone* **2011**, *49*, 944-954.
57. Akkiraju, H.; Bonor, J.; Nohe, A. CK2. 1, a novel peptide, induces articular cartilage formation in vivo. *Journal of Orthopaedic Research* **2017**, *35*, 876-885.

58. Akkiraju, H.; Bonor, J.; Olli, K.; Bowen, C.; Bragdon, B.; Coombs, H.; Donahue, L.R.; Duncan, R.; Nohe, A. Systemic injection of CK2. 3, a novel peptide acting downstream of bone morphogenetic protein receptor BMPRIa, leads to increased trabecular bone mass. *Journal of Orthopaedic Research* **2015**, *33*, 208-215.
59. Alkhiary, Y.M.; Gerstenfeld, L.C.; Krall, E.; Westmore, M.; Sato, M.; Mitlak, B.H.; Einhorn, T.A. Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1-34). *JBJS* **2005**, *87*, 731-741.
60. Komrakova, M.; Stuermer, E.K.; Werner, C.; Wicke, M.; Kolios, L.; Sehmisch, S.; Tezval, M.; Daub, F.; Martens, T.; Witzhausen, P. Effect of human parathyroid hormone hPTH (1-34) applied at different regimes on fracture healing and muscle in ovariectomized and healthy rats. *Bone* **2010**, *47*, 480-492.
61. Mognetti, B.; Marino, S.; Barberis, A.; Bravo Martin, A.-S.; Bala, Y.; Di Carlo, F.; Boivin, G.; Portigliatti Barbos, M. Experimental stimulation of bone healing with teriparatide: histomorphometric and microhardness analysis in a mouse model of closed fracture. *Calcified tissue international* **2011**, *89*, 163-171.
62. Chintamaneni, S.; Finzel, K.; Gruber, B. Successful treatment of sternal fracture nonunion with teriparatide. *Osteoporosis international* **2010**, *21*, 1059-1063.
63. Whitfield, J.F.; Motley, P.; Willick, G.E. Parathyroid hormone, its fragments and their analogs for the treatment of osteoporosis. *Treatments in Endocrinology* **2002**, *1*, 175-190.
64. Peggion, E.; Mammi, S.; Schievano, E.; Silvestri, L.; Schiebler, L.; Bisello, A.; Rosenblatt, M.; Chorev, M. Structure-Function Studies of Analogues of Parathyroid Hormone (PTH)-1-34 Containing β -Amino Acid Residues in Positions 11-13. *Biochemistry* **2002**, *41*, 8162-8175.
65. de Castro, L.F.; Lozano, D.; Portal-Núñez, S.; Maycas, M.; De la Fuente, M.; Caeiro, J.R.; Esbrit, P. Comparison of the skeletal effects induced by daily administration of PTHrP (1-36) and PTHrP (107-139) to ovariectomized mice. *Journal of cellular physiology* **2012**, *227*, 1752-1760.
66. Trejo, C.G.; Lozano, D.; Manzano, M.; Doadrio, J.C.; Salinas, A.J.; Dapía, S.; Gómez-Barrena, E.; Vallet-Regí, M.; García-Honduvilla, N.; Buján, J. The osteoinductive properties of mesoporous silicate coated with osteostatin in a rabbit femur cavity defect model. *Biomaterials* **2010**, *31*, 8564-8573.
67. Mrak, E.; Guidobono, F.; Moro, G.; Fraschini, G.; Rubinacci, A.; Villa, I. Calcitonin gene-related peptide (CGRP) inhibits apoptosis in human osteoblasts by β -catenin stabilization. *Journal of cellular physiology* **2010**, *225*, 701-708.
68. Villa, I.; Melzi, R.; Pagani, F.; Ravasi, F.; Rubinacci, A.; Guidobono, F. Effects of calcitonin gene-related peptide and amylin on human osteoblast-like cells proliferation. *European journal of pharmacology* **2000**, *409*, 273-278.
69. Wang, L.; Shi, X.; Zhao, R.; Halloran, B.P.; Clark, D.J.; Jacobs, C.R.; Kingery, W.S. Calcitonin-gene-related peptide stimulates stromal cell osteogenic differentiation and inhibits RANKL induced NF- κ B activation, osteoclastogenesis and bone resorption. *Bone* **2010**, *46*, 1369-1379.
70. Xu, G.; Jiang, D. The role and mechanism of exogenous calcitonin gene-related peptide on mesenchymal stem cell proliferation and osteogenic formation. *Cell biochemistry and biophysics* **2014**, *69*, 369-378.
71. Calland, J.W.; Harris, S.E.; Carnes Jr, D.L. Human pulp cells respond to calcitonin gene-related peptide in vitro. *Journal of endodontics* **1997**, *23*, 485-489.
72. Vignery, A.; McCarthy, T. The neuropeptide calcitonin gene-related peptide stimulates insulin-like growth factor I production by primary fetal rat osteoblasts. *Bone* **1996**, *18*, 331-335.
73. Ballica, R.; Valentijn, K.; Khachatryan, A.; Guerder, S.; Kapadia, S.; Gundberg, C.; Gilligan, J.; Flavell, R.A.; Vignery, A. Targeted expression of calcitonin gene-related peptide to osteoblasts increases bone density in mice. *Journal of bone and mineral research* **1999**, *14*, 1067-1074.
74. Bab, I.; Gazit, D.; Chorev, M.; Muhlrad, A.; Shteyer, A.; Greenberg, Z.; Namdar, M.; Kahn, A. Histone H4-related osteogenic growth peptide (OGP): a novel circulating stimulator of osteoblastic activity. *The EMBO journal* **1992**, *11*, 1867-1873.
75. Gabet, Y.; Müller, R.; Regev, E.; Sela, J.; Shteyer, A.; Salisbury, K.; Chorev, M.; Bab, I. Osteogenic growth peptide modulates fracture callus structural and mechanical properties. *Bone* **2004**, *35*, 65-73.
76. Brager, M.A.; Patterson, M.J.; Connolly, J.F.; Nevo, Z. Osteogenic growth peptide normally stimulated by blood loss and marrow ablation has local and systemic effects on fracture healing in rats. *Journal of Orthopaedic Research* **2000**, *18*, 133-139.
77. Fei, Q.; Guo, C.; Xu, X.; Gao, J.; Zhang, J.; Chen, T.; Cui, D. Osteogenic growth peptide enhances the proliferation of bone marrow mesenchymal stem cells from osteoprotegerin-deficient mice by CDK2/cyclin A. *Acta Biochim Biophys Sin* **2010**, *42*, 801-806.
78. An, G.; Xue, Z.; Zhang, B.; Deng, Q.; Wang, Y.; Lv, S. Expressing osteogenic growth peptide in the rabbit bone mesenchymal stem cells increased alkaline phosphatase activity and enhanced the collagen accumulation. *Eur Rev Med Pharmacol Sci* **2014**, *18*, 1618-1624.

79. Li, G.; Cui, Y.; McLmurray, L.; Allen, W.E.; Wang, H. rhBMP-2, rhVEGF165, rhPTN and thrombin-related peptide, TP508 induce chemotaxis of human osteoblasts and microvascular endothelial cells. *Journal of orthopaedic research* **2005**, *23*, 680-685.
80. Vordemvenne, T.; Paletta, J.R.; Hartensuer, R.; Pap, T.; Raschke, M.J.; Ochman, S. Cooperative effects in differentiation and proliferation between PDGF-BB and matrix derived synthetic peptides in human osteoblasts. *BMC musculoskeletal disorders* **2011**, *12*, 1-7.
81. Olszewska-Pazdrak, B.; Carney, D.H. Systemic administration of thrombin peptide TP508 enhances VEGF-stimulated angiogenesis and attenuates effects of chronic hypoxia. *Journal of vascular research* **2013**, *50*, 186-196.
82. Hanratty, B.M.; Ryaby, J.T.; Pan, X.-H.; Li, G. Thrombin related peptide TP508 promoted fracture repair in a mouse high energy fracture model. *Journal of Orthopaedic Surgery and Research* **2009**, *4*, 1-10.
83. Li, X.; Wang, H.; Touma, E.; Qi, Y.; Rousseau, E.; Quigg, R.J.; Ryaby, J.T. TP508 accelerates fracture repair by promoting cell growth over cell death. *Biochemical and biophysical research communications* **2007**, *364*, 187-193.
84. Wang, H.; Li, X.; Tomin, E.; Doty, S.B.; Lane, J.M.; Carney, D.H.; Ryaby, J.T. Thrombin peptide (TP508) promotes fracture repair by up-regulating inflammatory mediators, early growth factors, and increasing angiogenesis. *Journal of orthopaedic research* **2005**, *23*, 671-679.
85. Kim, Y.-J.; Park, Y.-J.; Lee, Y.-M.; Rhyu, I.-C.; Ku, Y. The biological effects of fibrin-binding synthetic oligopeptides derived from fibronectin on osteoblast-like cells. *Journal of Periodontal & Implant Science* **2012**, *42*, 113-118.
86. Lee, J.-A.; Ku, Y.; Rhyu, I.-C.; Chung, C.-P.; Park, Y.-J. Effects of fibrin-binding oligopeptide on osteopromotion in rabbit calvarial defects. *Journal of periodontal & implant science* **2010**, *40*, 211-219.
87. Martino, M.M.; Tortelli, F.; Mochizuki, M.; Traub, S.; Ben-David, D.; Kuhn, G.A.; Müller, R.; Livne, E.; Eming, S.A.; Hubbell, J.A. Engineering the growth factor microenvironment with fibronectin domains to promote wound and bone tissue healing. *Science translational medicine* **2011**, *3*, 100ra189-100ra189.
88. Lee, J.-Y.; Choo, J.-E.; Park, H.-J.; Park, J.-B.; Lee, S.-C.; Jo, I.; Lee, S.-J.; Chung, C.-P.; Park, Y.-J. Injectable gel with synthetic collagen-binding peptide for enhanced osteogenesis in vitro and in vivo. *Biochemical and biophysical research communications* **2007**, *357*, 68-74.
89. Shin, M.K.; Kim, M.-K.; Bae, Y.-S.; Jo, I.; Lee, S.-J.; Chung, C.-P.; Park, Y.-J. A novel collagen-binding peptide promotes osteogenic differentiation via Ca²⁺/calmodulin-dependent protein kinase II/ERK/AP-1 signaling pathway in human bone marrow-derived mesenchymal stem cells. *Cellular signalling* **2008**, *20*, 613-624.
90. Lee, J.-Y.; Choo, J.-E.; Choi, Y.-S.; Park, J.-B.; Min, D.-S.; Lee, S.-J.; Rhyu, H.K.; Jo, I.-H.; Chung, C.-P.; Park, Y.-J. Assembly of collagen-binding peptide with collagen as a bioactive scaffold for osteogenesis in vitro and in vivo. *Biomaterials* **2007**, *28*, 4257-4267.
91. Egusa, H.; Kaneda, Y.; Akashi, Y.; Hamada, Y.; Matsumoto, T.; Saeki, M.; Thakor, D.K.; Tabata, Y.; Matsuura, N.; Yatani, H. Enhanced bone regeneration via multimodal actions of synthetic peptide SVVYGLR on osteoprogenitors and osteoclasts. *Biomaterials* **2009**, *30*, 4676-4686.
92. Hamada, Y.; Yuki, K.; Okazaki, M.; Fujitani, W.; Matsumoto, T.; Hashida, M.K.; Harutsugu, K.; Nokihara, K.; Daito, M.; Matsuura, N. Osteopontin-derived peptide SVVYGLR induces angiogenesis in vivo. *Dental materials journal* **2004**, *23*, 650-655.
93. Park, K.M.; Lee, Y.; Son, J.Y.; Bae, J.W.; Park, K.D. In situ SVVYGLR peptide conjugation into injectable gelatin-poly (ethylene glycol)-tyramine hydrogel via enzyme-mediated reaction for enhancement of endothelial cell activity and neo-vascularization. *Bioconjugate chemistry* **2012**, *23*, 2042-2050.
94. Rezaian, A.; Healy, K.E. Biomimetic peptide surfaces that regulate adhesion, spreading, cytoskeletal organization, and mineralization of the matrix deposited by osteoblast-like cells. *Biotechnology progress* **1999**, *15*, 19-32.
95. Stile, R.A.; Healy, K.E. Thermo-responsive peptide-modified hydrogels for tissue regeneration. *Biomacromolecules* **2001**, *2*, 185-194.
96. Van Hove, A.H.; Benoit, D.S. Depot-based delivery systems for pro-angiogenic peptides: a review. *Frontiers in bioengineering and biotechnology* **2015**, *3*, 102.
97. Finetti, F.; Basile, A.; Capasso, D.; Di Gaetano, S.; Di Stasi, R.; Pascale, M.; Turco, C.M.; Ziche, M.; Morbidelli, L.; D'Andrea, L.D. Functional and pharmacological characterization of a VEGF mimetic peptide on reparative angiogenesis. *Biochemical pharmacology* **2012**, *84*, 303-311.
98. Chen, R.R.; Silva, E.A.; Yuen, W.W.; Mooney, D.J. Spatio-temporal VEGF and PDGF delivery patterns blood vessel formation and maturation. *Pharmaceutical research* **2007**, *24*, 258-264.
99. Kang, H.-M.; Kang, Y.; Chun, H.J.; Jeong, J.-W.; Park, C. Evaluation of the in vitro and in vivo angiogenic effects of exendin-4. *Biochemical and biophysical research communications* **2013**, *434*, 150-154.

100. Hamada, Y.; Nokihara, K.; Okazaki, M.; Fujitani, W.; Matsumoto, T.; Matsuo, M.; Umakoshi, Y.; Takahashi, J.; Matsuura, N. Angiogenic activity of osteopontin-derived peptide SVVYGLR. *Biochemical and biophysical research communications* **2003**, *310*, 153-157.
101. Hamada, Y.; Egusa, H.; Kaneda, Y.; Hirata, I.; Kawaguchi, N.; Hirao, T.; Matsumoto, T.; Yao, M.; Daito, K.; Suzuki, M. Synthetic osteopontin-derived peptide SVVYGLR can induce neovascularization in artificial bone marrow scaffold biomaterials. *Dental materials journal* **2007**, *26*, 487-492.
102. Lane, T.F.; Iruela-Arispe, M.L.; Johnson, R.S.; Sage, E.H. SPARC is a source of copper-binding peptides that stimulate angiogenesis. *The Journal of cell biology* **1994**, *125*, 929-943.
103. Van Hove, A.H.; Burke, K.; Antonienko, E.; Brown III, E.; Benoit, D.S. Enzymatically-responsive pro-angiogenic peptide-releasing poly (ethylene glycol) hydrogels promote vascularization in vivo. *Journal of Controlled Release* **2015**, *217*, 191-201.
104. Hardy, B.; Raiter, A.; Weiss, C.; Kaplan, B.; Tenenbaum, A.; Battler, A. Angiogenesis induced by novel peptides selected from a phage display library by screening human vascular endothelial cells under different physiological conditions. *Peptides* **2007**, *28*, 691-701.
105. Wang, W.; Rigueur, D.; Lyons, K.M. TGF β signaling in cartilage development and maintenance. *Birth Defects Research Part C: Embryo Today: Reviews* **2014**, *102*, 37-51.
106. Bhatnagar, R.S.; Qian, J.J. Peptide compositions with growth factor-like activity. **1997**.
107. Renner, J.N.; Liu, J.C. Investigating the effect of peptide agonists on the chondrogenic differentiation of human mesenchymal stem cells using design of experiments. *Biotechnology Progress* **2013**, *29*, 1550-1557.
108. Zhang, Z.; Gupte, M.J.; Jin, X.; Ma, P.X. Injectable peptide decorated functional nanofibrous hollow microspheres to direct stem cell differentiation and tissue regeneration. *Advanced functional materials* **2015**, *25*, 350-360.
109. Mittal, A.; Kumar, R.; Parsad, D.; Kumar, N. Cytomodulin-functionalized porous PLGA particulate scaffolds respond better to cell migration, actin production and wound healing in rodent model. *Journal of tissue engineering and regenerative medicine* **2014**, *8*, 351-363.
110. Zhao, B.; Yang, D.; Wong, J.H.; Wang, J.; Yin, C.; Zhu, Y.; Fan, S.; Ng, T.B.; Xia, J.; Li, Z. A Thioether-Stabilized d-Proline-l-Proline-Induced β -Hairpin Peptide of Defensin Segment Increases Its Anti-Candida albicans Ability. *ChemBioChem* **2016**, *17*, 1416-1420.
111. Ruczynski, J.; Wierzbicki, P.M.; Kogut-Wierzbicka, M.; Mucha, P.; Siedlecka-Kroplewska, K.; Rekowski, P. Cell-penetrating peptides as a promising tool for delivery of various molecules into the cells. *Folia histochemica et cytobiologica* **2014**, *52*, 257-269.
112. Akkiraju, H.; Srinivasan, P.P.; Xu, X.; Jia, X.; Safran, C.B.K.; Nohe, A. CK2. 1, a bone morphogenetic protein receptor type Ia mimetic peptide, repairs cartilage in mice with destabilized medial meniscus. *Stem Cell Research & Therapy* **2017**, *8*, 1-11.
113. Renner, J.N.; Kim, Y.; Liu, J.C. Bone morphogenetic protein-derived peptide promotes chondrogenic differentiation of human mesenchymal stem cells. *Tissue Engineering Part A* **2012**, *18*, 2581-2589.
114. Scholz, M.; Schleicher, P.; Sewing, A.; Gelinsky, M.; Kandziora, F. Cyclic-RGD is as effective as rhBMP-2 in anterior interbody fusion of the sheep cervical spine. *Spine* **2013**, *38*, E59-E65.
115. Hennessy, K.M.; Pollot, B.E.; Clem, W.C.; Phipps, M.C.; Sawyer, A.A.; Culpepper, B.K.; Bellis, S.L. The effect of collagen I mimetic peptides on mesenchymal stem cell adhesion and differentiation, and on bone formation at hydroxyapatite surfaces. *Biomaterials* **2009**, *30*, 1898-1909.
116. Sawyer, A.A.; Hennessy, K.M.; Bellis, S.L. The effect of adsorbed serum proteins, RGD and proteoglycan-binding peptides on the adhesion of mesenchymal stem cells to hydroxyapatite. *Biomaterials* **2007**, *28*, 383-392.
117. Mas-Moruno, C.; Fraioli, R.; Albericio, F.; Manero, J.M.; Gil, F.J. Novel peptide-based platform for the dual presentation of biologically active peptide motifs on biomaterials. *ACS applied materials & interfaces* **2014**, *6*, 6525-6536.
118. Paredes, V.; Salvagni, E.; Rodríguez-Castellon, E.; Gil, F.; Manero, J. Study on the use of 3-aminopropyltriethoxysilane and 3-chloropropyltriethoxysilane to surface biochemical modification of a novel low elastic modulus Ti-Nb-Hf alloy. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* **2015**, *103*, 495-502.
119. Benoit, D.S.; Anseth, K.S. The effect on osteoblast function of colocalized RGD and PHSRN epitopes on PEG surfaces. *Biomaterials* **2005**, *26*, 5209-5220.
120. Schuler, M.; Hamilton, D.W.; Kunzler, T.P.; Sprecher, C.M.; de Wild, M.; Brunette, D.M.; Textor, M.; Tosatti, S.G. Comparison of the response of cultured osteoblasts and osteoblasts outgrown from rat calvarial bone chips to nonfouling KRSR and FHRRIKA-peptide modified rough titanium surfaces. *Journal of Biomedical Materials Research Part B: Applied Biomaterials: An Official Journal of The Society for Biomaterials, The Japanese*

- Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials* **2009**, 91, 517-527.
121. Dee, K.C.; Andersen, T.T.; Bizios, R. Design and function of novel osteoblast-adhesive peptides for chemical modification of biomaterials. *Journal of biomedical materials research* **1998**, 40, 371-377.
 122. Palchesko, R.N.; Romeo, J.D.; McGowan, K.A.; Gawalt, E.S. Increased osteoblast adhesion on physically optimized KRSR modified calcium aluminate. *Journal of Biomedical Materials Research Part A* **2012**, 100, 1229-1238.
 123. Sun, S.; Yu, W.; Zhang, Y.; Zhang, F. Increased preosteoblast adhesion and osteogenic gene expression on TiO₂ nanotubes modified with KRSR. *Journal of Materials Science: Materials in Medicine* **2013**, 24, 1079-1091.
 124. Nelson, M.; Balasundaram, G.; Webster, T.J. Increased osteoblast adhesion on nanoparticulate crystalline hydroxyapatite functionalized with KRSR. *International journal of nanomedicine* **2006**, 1, 339.
 125. Balasundaram, G.; Webster, T.J. Increased osteoblast adhesion on nanogained Ti modified with KRSR. *Journal of Biomedical Materials Research Part A* **2007**, 80, 602-611.
 126. Frith, J.E.; Mills, R.J.; Hudson, J.E.; Cooper-White, J.J. Tailored integrin–extracellular matrix interactions to direct human mesenchymal stem cell differentiation. *Stem cells and development* **2012**, 21, 2442-2456.
 127. Mohammed, M.; Lai, T.-S.; Lin, H.-C. Substrate stiffness and sequence dependent bioactive peptide hydrogels influence the chondrogenic differentiation of human mesenchymal stem cells. *Journal of Materials Chemistry B* **2021**, 9, 1676-1685.
 128. Li, R.; Xu, J.; Wong, D.S.H.; Li, J.; Zhao, P.; Bian, L. Self-assembled N-cadherin mimetic peptide hydrogels promote the chondrogenesis of mesenchymal stem cells through inhibition of canonical Wnt/ β -catenin signaling. *Biomaterials* **2017**, 145, 33-43.
 129. Zhu, M.; Lin, S.; Sun, Y.; Feng, Q.; Li, G.; Bian, L. Hydrogels functionalized with N-cadherin mimetic peptide enhance osteogenesis of hMSCs by emulating the osteogenic niche. *Biomaterials* **2016**, 77, 44-52.
 130. Li, W.; Yu, B.; Li, M.; Sun, D.; Hu, Y.; Zhao, M.; Cui, C.-B.; Hou, S. NEMO-binding domain peptide promotes osteoblast differentiation impaired by tumor necrosis factor alpha. *Biochemical and biophysical research communications* **2010**, 391, 1228-1233.
 131. Dai, S.; Hirayama, T.; Abbas, S.; Abu-Amer, Y. The I κ B kinase (IKK) inhibitor, NEMO-binding domain peptide, blocks osteoclastogenesis and bone erosion in inflammatory arthritis. *Journal of Biological Chemistry* **2004**, 279, 37219-37222.
 132. Ligorio, C.; Mata, A. Synthetic extracellular matrices with function-encoding peptides. *Nature Reviews Bioengineering* **2023**, 1-19.
 133. Lin, H.; Zhou, J.; Shen, L.; Ruan, Y.; Dong, J.; Guo, C.; Chen, Z. Biotin-conjugated anti-CD44 antibody–avidin binding system for the improvement of chondrocyte adhesion to scaffolds. *Journal of Biomedical Materials Research Part A* **2014**, 102, 1140-1148.
 134. Cheung, C.S.; Lui, J.C.; Baron, J. Identification of chondrocyte-binding peptides by phage display. *Journal of Orthopaedic research* **2013**, 31, 1053-1058.
 135. Shao, Z.; Zhang, X.; Pi, Y.; Wang, X.; Jia, Z.; Zhu, J.; Dai, L.; Chen, W.; Yin, L.; Chen, H. Polycaprolactone electrospun mesh conjugated with an MSC affinity peptide for MSC homing in vivo. *Biomaterials* **2012**, 33, 3375-3387.
 136. Webb, D.J.; Roadcap, D.W.; Dhakephalkar, A.; Gonias, S.L. A 16-amino acid peptide from human α 2-macroglobulin binds transforming growth factor- β and platelet-derived growth factor-BB. *Protein Science* **2000**, 9, 1986-1992.
 137. Shah, R.N.; Shah, N.A.; Del Rosario Lim, M.M.; Hsieh, C.; Nuber, G.; Stupp, S.I. Supramolecular design of self-assembling nanofibers for cartilage regeneration. *Proceedings of the National Academy of Sciences* **2010**, 107, 3293-3298.
 138. Thakkar, S.; Fernandes, H.; Moroni, L. Decellularized extracellular matrix scaffolds for cartilage regeneration. *Cartilage Tissue Engineering: Methods and Protocols* **2015**, 133-151.
 139. Masters, K.S.; Shah, D.N.; Leinwand, L.A.; Anseth, K.S. Crosslinked hyaluronan scaffolds as a biologically active carrier for valvular interstitial cells. *Biomaterials* **2005**, 26, 2517-2525.
 140. Parmar, P.A.; Chow, L.W.; St-Pierre, J.-P.; Horejs, C.-M.; Peng, Y.Y.; Werkmeister, J.A.; Ramshaw, J.A.; Stevens, M.M. Collagen-mimetic peptide-modifiable hydrogels for articular cartilage regeneration. *Biomaterials* **2015**, 54, 213-225.
 141. Ruoslahti, E.; Pierschbacher, M.D. Arg-Gly-Asp: a versatile cell recognition signal. *Cell* **1986**, 44, 517-518.
 142. Kim, H.D.; Heo, J.; Hwang, Y.; Kwak, S.-Y.; Park, O.K.; Kim, H.; Varghese, S.; Hwang, N.S. Extracellular-matrix-based and Arg-Gly-Asp–modified photopolymerizing hydrogels for cartilage tissue engineering. *Tissue Engineering Part A* **2015**, 21, 757-766.
 143. Jeschke, B.; Meyer, J.; Jonczyk, A.; Kessler, H.; Adamietz, P.; Meenen, N.M.; Kantlehner, M.; Goepfert, C.; Nies, B. RGD-peptides for tissue engineering of articular cartilage. *Biomaterials* **2002**, 23, 3455-3463.

144. Kim, I.L.; Khetan, S.; Baker, B.M.; Chen, C.S.; Burdick, J.A. Fibrous hyaluronic acid hydrogels that direct MSC chondrogenesis through mechanical and adhesive cues. *Biomaterials* **2013**, *34*, 5571-5580.
145. Homandberg, G.A.; Hui, F. Arg-Gly-Asp-Ser peptide analogs suppress cartilage chondrolytic activities of integrin-binding and nonbinding fibronectin fragments. *Archives of biochemistry and biophysics* **1994**, *310*, 40-48.
146. Zhang, T.; Wen, F.; Wu, Y.; Goh, G.S.H.; Ge, Z.; Tan, L.P.; Hui, J.H.P.; Yang, Z. Cross-talk between TGF-beta/SMAD and integrin signaling pathways in regulating hypertrophy of mesenchymal stem cell chondrogenesis under deferral dynamic compression. *Biomaterials* **2015**, *38*, 72-85.
147. Park, J.-W.; Kurashima, K.; Tustusmi, Y.; An, C.-H.; Suh, J.-Y.; Doi, H.; Nomura, N.; Noda, K.; Hanawa, T. Bone healing of commercial oral implants with RGD immobilization through electrodeposited poly (ethylene glycol) in rabbit cancellous bone. *Acta Biomaterialia* **2011**, *7*, 3222-3229.
148. Tavella, S.; Raffo, P.; Tacchetti, C.; Cancedda, R.; Castagnola, P. N-CAM and N-cadherin expression during in vitro chondrogenesis. *Experimental cell research* **1994**, *215*, 354-362.
149. Bian, L.; Guvendiren, M.; Mauck, R.L.; Burdick, J.A. Hydrogels that mimic developmentally relevant matrix and N-cadherin interactions enhance MSC chondrogenesis. *Proceedings of the National Academy of Sciences* **2013**, *110*, 10117-10122.
150. Kuo, Y.-C.; Wang, C.-C. Surface modification with peptide for enhancing chondrocyte adhesion and cartilage regeneration in porous scaffolds. *Colloids and Surfaces B: Biointerfaces* **2011**, *84*, 63-70.
151. Jo, J.; Song, H.; Park, S.G.; Lee, S.H.; Ko, J.J.; Park, J.H.; Jeong, J.; Cheon, Y.P.; Lee, D.R. Regulation of Differentiation Potential of Human Mesenchymal Stem Cells by Intracytoplasmic Delivery of Coactivator-Associated Arginine Methyltransferase 1 Protein Using Cell-Penetrating Peptide. *Stem Cells* **2012**, *30*, 1703-1713.
152. Suh, J.S.; Lee, J.Y.; Choi, Y.J.; You, H.K.; Hong, S.-D.; Chung, C.P.; Park, Y.J. Intracellular delivery of cell-penetrating peptide-transcriptional factor fusion protein and its role in selective osteogenesis. *International journal of nanomedicine* **2014**, 1153-1166.
153. Park, S.; Doh, J.; Park, S.; Lim, J.; Kim, S.; Youn, J.; Jin, H.; Seo, S.; Song, M.; Sung, S. Branched oligomerization of cell-permeable peptides markedly enhances the transduction efficiency of adenovirus into mesenchymal stem cells. *Gene therapy* **2010**, *17*, 1052-1061.
154. Guo, X.; Chu, X.; Li, W.; Pan, Q.; You, H. Chondrogenic effect of precartilaginous stem cells following NLS-TAT cell penetrating peptide-assisted transfection of eukaryotic h TGF β 3. *Journal of Cellular Biochemistry* **2013**, *114*, 2588-2594.
155. Pan, Q.; Li, W.; Yuan, X.; Rakhmanov, Y.; Wang, P.; Lu, R.; Mao, Z.; Shang, X.; You, H. Chondrogenic effect of cell-based scaffold of self-assembling peptides/PLGA-PLL loading the hTGF β 3 plasmid DNA. *Journal of Materials Science: Materials in Medicine* **2016**, *27*, 1-11.
156. Trepatt, X.; Chen, Z.; Jacobson, K. Cell migration. *Comprehensive Physiology* **2012**, *2*, 2369.
157. Shen, W.; Chen, X.; Chen, J.; Yin, Z.; Heng, B.C.; Chen, W.; Ouyang, H.-W. The effect of incorporation of exogenous stromal cell-derived factor-1 alpha within a knitted silk-collagen sponge scaffold on tendon regeneration. *Biomaterials* **2010**, *31*, 7239-7249.
158. Yeboah, A.; Cohen, R.I.; Faulknor, R.; Schloss, R.; Yarmush, M.L.; Berthiaume, F. The development and characterization of SDF1 α -elastin-like-peptide nanoparticles for wound healing. *Journal of controlled release* **2016**, *232*, 238-247.
159. Torres, P.; Díaz, J.; Arce, M.; Silva, P.; Mendoza, P.; Lois, P.; Molina-Berrios, A.; Owen, G.I.; Palma, V.; Torres, V.A. The salivary peptide histatin-1 promotes endothelial cell adhesion, migration, and angiogenesis. *The FASEB Journal* **2017**, *31*, 4946-4958.
160. Huang, J.J.; Xia, C.J.; Wei, Y.; Yao, Y.; Dong, M.W.; Lin, K.Z.; Yu, L.S.; Gao, Y.; Fan, Y.Y. Annexin A1-derived peptide Ac2-26 facilitates wound healing in diabetic mice. *Wound Repair and Regeneration* **2020**, *28*, 772-779.
161. Di Grazia, A.; Cappiello, F.; Imanishi, A.; Mastrofrancesco, A.; Picardo, M.; Paus, R.; Mangoni, M.L. The frog skin-derived antimicrobial peptide esculentin-1a (1-21) NH2 promotes the migration of human HaCaT keratinocytes in an EGF receptor-dependent manner: a novel promoter of human skin wound healing? *PloS one* **2015**, *10*, e0128663.
162. Kuroda, K.; Okumura, K.; Isogai, H.; Isogai, E. The human cathelicidin antimicrobial peptide LL-37 and mimics are potential anticancer drugs. *Frontiers in oncology* **2015**, *5*, 144.
163. Rubert Pérez, C.M.; Álvarez, Z.; Chen, F.; Aytun, T.; Stupp, S.I. Mimicking the bioactivity of fibroblast growth factor-2 using supramolecular nanoribbons. *ACS Biomaterials Science & Engineering* **2017**, *3*, 2166-2175.
164. Zhang, S. Emerging biological materials through molecular self-assembly. *Biotechnology advances* **2002**, *20*, 321-339.

165. Ryan, D.M.; Nilsson, B.L. Self-assembled amino acids and dipeptides as noncovalent hydrogels for tissue engineering. *Polymer Chemistry* **2012**, *3*, 18-33.
166. Avinash, M.; Govindaraju, T. Nanoarchitectonics of biomolecular assemblies for functional applications. *Nanoscale* **2014**, *6*, 13348-13369.
167. Lee, J.Y.; Choo, J.E.; Choi, Y.S.; Lee, K.Y.; Min, D.S.; Pi, S.H.; Seol, Y.J.; Lee, S.J.; Jo, I.H.; Chung, C.P. Characterization of the surface immobilized synthetic heparin binding domain derived from human fibroblast growth factor-2 and its effect on osteoblast differentiation. *Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials* **2007**, *83*, 970-979.
168. Furuya, Y.; Inagaki, A.; Khan, M.; Mori, K.; Penninger, J.M.; Nakamura, M.; Udagawa, N.; Aoki, K.; Ohya, K.; Uchida, K. Stimulation of bone formation in cortical bone of mice treated with a receptor activator of nuclear factor- κ B ligand (RANKL)-binding peptide that possesses osteoclastogenesis inhibitory activity. *Journal of Biological Chemistry* **2013**, *288*, 5562-5571.
169. Ikeno, M.; Hibi, H.; Kinoshita, K.; Hattori, H.; Ueda, M. Effects of self-assembling peptide hydrogel scaffold on bone regeneration with recombinant human bone morphogenetic protein-2. *Oral & Craniofacial Tissue Engineering* **2011**, *1*.
170. Recha-Sancho, L.; Semino, C.E. Heparin-based self-assembling peptide scaffold reestablish chondrogenic phenotype of expanded de-differentiated human chondrocytes. *Journal of Biomedical Materials Research Part A* **2016**, *104*, 1694-1706.
171. Yamaoka, H.; Asato, H.; Ogasawara, T.; Nishizawa, S.; Takahashi, T.; Nakatsuka, T.; Koshima, I.; Nakamura, K.; Kawaguchi, H.; Chung, U.I. Cartilage tissue engineering using human auricular chondrocytes embedded in different hydrogel materials. *Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials* **2006**, *78*, 1-11.
172. Kisiday, J.; Jin, M.; Kurz, B.; Hung, H.; Semino, C.; Zhang, S.; Grodzinsky, A. Self-assembling peptide hydrogel fosters chondrocyte extracellular matrix production and cell division: implications for cartilage tissue repair. *Proceedings of the National Academy of Sciences* **2002**, *99*, 9996-10001.
173. Sridhar, B.V.; Brock, J.L.; Silver, J.S.; Leight, J.L.; Randolph, M.A.; Anseth, K.S. Development of a cellularly degradable PEG hydrogel to promote articular cartilage extracellular matrix deposition. *Advanced healthcare materials* **2015**, *4*, 702-713.
174. Bin Hafeez, A.; Jiang, X.; Bergen, P.J.; Zhu, Y. Antimicrobial peptides: An update on classifications and databases. *International journal of molecular sciences* **2021**, *22*, 11691.
175. Hao, Z.; Chen, R.; Chai, C.; Wang, Y.; Chen, T.; Li, H.; Hu, Y.; Feng, Q.; Li, J. Antimicrobial peptides for bone tissue engineering: Diversity, effects and applications. *Frontiers in Bioengineering and Biotechnology* **2022**, *10*, 1030162.
176. Sun, Y.; Chan, J.; Bose, K.; Tam, C. Simultaneous control of infection and inflammation with keratin-derived antibacterial peptides targeting TLRs and co-receptors. *Science Translational Medicine* **2023**, *15*, eade2909.
177. de Leeuw, E.; Li, C.; Zeng, P.; Li, C.; Diepeveen-de Buin, M.; Lu, W.-Y.; Breukink, E.; Lu, W. Functional interaction of human neutrophil peptide-1 with the cell wall precursor lipid II. *FEBS letters* **2010**, *584*, 1543-1548.
178. Wenzel, M.; Chiriac, A.I.; Otto, A.; Zweytick, D.; May, C.; Schumacher, C.; Gust, R.; Albada, H.B.; Penkova, M.; Krämer, U. Small cationic antimicrobial peptides delocalize peripheral membrane proteins. *Proceedings of the National Academy of Sciences* **2014**, *111*, E1409-E1418.
179. Park, C.B.; Kim, H.S.; Kim, S.C. Mechanism of action of the antimicrobial peptide buforin II: buforin II kills microorganisms by penetrating the cell membrane and inhibiting cellular functions. *Biochemical and biophysical research communications* **1998**, *244*, 253-257.
180. He, Y.; Jin, Y.; Wang, X.; Yao, S.; Li, Y.; Wu, Q.; Ma, G.; Cui, F.; Liu, H. An antimicrobial peptide-loaded gelatin/chitosan nanofibrous membrane fabricated by sequential layer-by-layer electrospinning and electrospraying techniques. *Nanomaterials* **2018**, *8*, 327.
181. Vallet-Regí, M.; Lozano, D.; González, B.; Izquierdo-Barba, I. Biomaterials against bone infection, Adv. Healthc. Mater. **9** (2020).
182. Tsai, P.-W.; Yang, C.-Y.; Chang, H.-T.; Lan, C.-Y. Human antimicrobial peptide LL-37 inhibits adhesion of *Candida albicans* by interacting with yeast cell-wall carbohydrates. *PloS one* **2011**, *6*, e17755.
183. De La Fuente-Núñez, C.; Korolik, V.; Bains, M.; Nguyen, U.; Breidenstein, E.B.; Horsman, S.; Lewenza, S.; Burrows, L.; Hancock, R.E. Inhibition of bacterial biofilm formation and swarming motility by a small synthetic cationic peptide. *Antimicrobial agents and chemotherapy* **2012**, *56*, 2696-2704.

184. Libardo, M.D.J.; Bahar, A.A.; Ma, B.; Fu, R.; McCormick, L.E.; Zhao, J.; McCallum, S.A.; Nussinov, R.; Ren, D.; Angeles-Boza, A.M. Nuclease activity gives an edge to host-defense peptide piscidin 3 over piscidin 1, rendering it more effective against persisters and biofilms. *The FEBS journal* **2017**, *284*, 3662-3683.
185. Luca, V.; Stringaro, A.; Colone, M.; Pini, A.; Mangoni, M.L. Esculentin (1-21), an amphibian skin membrane-active peptide with potent activity on both planktonic and biofilm cells of the bacterial pathogen *Pseudomonas aeruginosa*. *Cellular and molecular life sciences* **2013**, *70*, 2773-2786.
186. Chen, S.; Lu, Z.; Wang, F.; Wang, Y. Cathelicidin-WA polarizes E. coli K88-induced M1 macrophage to M2-like macrophage in RAW264. 7 cells. *International Immunopharmacology* **2018**, *54*, 52-59.
187. Dai, M.; Sui, B.; Xue, Y.; Liu, X.; Sun, J. Cartilage repair in degenerative osteoarthritis mediated by squid type II collagen via immunomodulating activation of M2 macrophages, inhibiting apoptosis and hypertrophy of chondrocytes. *Biomaterials* **2018**, *180*, 91-103.
188. Zhang, H.; Lin, C.; Zeng, C.; Wang, Z.; Wang, H.; Lu, J.; Liu, X.; Shao, Y.; Zhao, C.; Pan, J. Synovial macrophage M1 polarisation exacerbates experimental osteoarthritis partially through R-spondin-2. *Annals of the rheumatic diseases* **2018**, *77*, 1524-1534.
189. Wang, B.; Bian, A.; Jia, F.; Lan, J.; Yang, H.; Yan, K.; Xie, L.; Qiao, H.; Chang, X.; Lin, H. "Dual-functional" strontium titanate nanotubes designed based on fusion peptides simultaneously enhancing anti-infection and osseointegration. *Biomaterials Advances* **2022**, *133*, 112650.
190. Zhou, L.; Han, Y.; Ding, J.; Chen, X.; Huang, S.; Xing, X.; Wu, D.; Chen, J. Regulation of an antimicrobial peptide GL13K-modified titanium surface on osteogenesis, osteoclastogenesis, and angiogenesis base on osteoimmunology. *ACS Biomaterials Science & Engineering* **2021**, *7*, 4569-4580.
191. Liu, H.-W.; Wei, D.-X.; Deng, J.-Z.; Zhu, J.-J.; Xu, K.; Hu, W.-H.; Xiao, S.-H.; Zhou, Y.-G. Combined antibacterial and osteogenic in situ effects of a bifunctional titanium alloy with nanoscale hydroxyapatite coating. *Artificial cells, nanomedicine, and biotechnology* **2018**, *46*, 460-470.
192. Basu, S.; Kumar, M.; Chansuria, J.; Singh, T.B.; Bhatnagar, R.; Shukla, V.K. Effect of Cytomodulin-10 (TGF- β 1 analogue) on wound healing by primary intention in a murine model. *International Journal of Surgery* **2009**, *7*, 460-465.
193. Boda, S.K.; Wang, H.; John, J.V.; Reinhardt, R.A.; Xie, J. Dual delivery of alendronate and E7-BMP-2 peptide via calcium chelation to mineralized nanofiber fragments for alveolar bone regeneration. *ACS biomaterials science & engineering* **2020**, *6*, 2368-2375.
194. Laboy-López, S.; Méndez Fernández, P.O.; Padilla-Zayas, J.G.; Nicolau, E. Bioactive Cellulose Acetate Electrospun Mats as Scaffolds for Bone Tissue Regeneration. *International Journal of Biomaterials* **2022**, 2022.
195. Lukasova, V.; Buzgo, M.; Sovkova, V.; Dankova, J.; Rampichova, M.; Amler, E. Osteogenic differentiation of 3D cultured mesenchymal stem cells induced by bioactive peptides. *Cell Proliferation* **2017**, *50*, e12357.
196. Gentile, P.; Ferreira, A.M.; Callaghan, J.T.; Miller, C.A.; Atkinson, J.; Freeman, C.; Hatton, P.V. Multilayer nanoscale encapsulation of biofunctional peptides to enhance bone tissue regeneration in vivo. *Advanced healthcare materials* **2017**, *6*, 1601182.
197. Gentile, P.; Ghione, C.; Tonda-Turo, C.; Kalaskar, D. Peptide functionalisation of nanocomposite polymer for bone tissue engineering using plasma surface polymerisation. *RSC advances* **2015**, *5*, 80039-80047.
198. Shekaran, A.; García, A.J. Extracellular matrix-mimetic adhesive biomaterials for bone repair. *Journal of biomedical materials research Part A* **2011**, *96*, 261-272.
199. Hasenbein, M.; Andersen, T.; Bizios, R. Micropatterned surfaces modified with select peptides promote exclusive interactions with osteoblasts. *Biomaterials* **2002**, *23*, 3937-3942.
200. Posadowska, U.; Storm, I.; de Wolf, F.; van den Beucken, J.; Leeuwenburgh, S. Nanofibrillar hydrogel scaffolds from recombinant protein-based polymers with integrin-and proteoglycan-binding domains. *Production of protein-based polymers in Pichia pastoris* **1**, 135.
201. Reyes, C.D.; García, A.J. α 2 β 1 integrin-specific collagen-mimetic surfaces supporting osteoblastic differentiation. *Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials* **2004**, *69*, 591-600.
202. Yukna, R.A.; Callan, D.P.; Krauser, J.T.; Evans, G.H.; Aichelmann-Reidy, M.E.; Moore, K.; Cruz, R.; Scott, J.B. Multi-center clinical evaluation of combination anorganic bovine-derived hydroxyapatite matrix (ABM)/cell binding peptide (P-15) as a bone replacement graft material in human periodontal osseous defects. 6-month results. *Journal of periodontology* **1998**, *69*, 655-663.
203. Thorwarth, M.; Schultze-Mosgau, S.; Wehrhan, F.; Srouf, S.; Wiltfang, J.; Neukam, F.W.; Schlegel, K.A. Enhanced bone regeneration with a synthetic cell-binding peptide—in vivo results. *Biochemical and biophysical research communications* **2005**, *329*, 789-795.

204. Thorwarth, M.; Schultze-Mosgau, S.; Wehrhan, F.; Kessler, P.; Srouf, S.; Wiltfang, J.; Schlegel, K.A. Bioactivation of an anorganic bone matrix by P-15 peptide for the promotion of early bone formation. *Biomaterials* **2005**, *26*, 5648-5657.
205. Matos, S.; Guerra, F.; Krauser, J.T.; Figueiredo, H.; Marcelino, J.P.; Sanz, M. Evaluation of an anorganic bovine-derived mineral with P-15 hydrogel bone graft: preliminary study in a rabbit cranial bone model. *Clinical Oral Implants Research* **2012**, *23*, 698-705.
206. Culpepper, B.K.; Phipps, M.C.; Bonvallet, P.P.; Bellis, S.L. Enhancement of peptide coupling to hydroxyapatite and implant osseointegration through collagen mimetic peptide modified with a polyglutamate domain. *Biomaterials* **2010**, *31*, 9586-9594.
207. Wang, V.; Misra, G.; Amsden, B. Immobilization of a bone and cartilage stimulating peptide to a synthetic bone graft. *Journal of Materials Science: Materials in Medicine* **2008**, *19*, 2145-2155.
208. Shuqiang, M.; Kunzheng, W.; Xiaoqiang, D.; Wei, W.; Mingyu, Z.; Daocheng, W. Osteogenic growth peptide incorporated into PLGA scaffolds accelerates healing of segmental long bone defects in rabbits. *Journal of plastic, reconstructive & aesthetic surgery* **2008**, *61*, 1558-1560.
209. Jung, R.E.; Hämmerle, C.H.; Kokovic, V.; Weber, F.E. Bone regeneration using a synthetic matrix containing a parathyroid hormone peptide combined with a grafting material. *International Journal of Oral & Maxillofacial Implants* **2007**, *22*.
210. Sheller, M.R.; Crowther, R.S.; Kinney, J.H.; Yang, J.; Di Jorio, S.; Breunig, T.; Carney, D.H.; Ryaby, J.T. Repair of rabbit segmental defects with the thrombin peptide, TP508. *Journal of orthopaedic research* **2004**, *22*, 1094-1099.
211. Rammelt, S.; Illert, T.; Bierbaum, S.; Scharnweber, D.; Zwipp, H.; Schneiders, W. Coating of titanium implants with collagen, RGD peptide and chondroitin sulfate. *Biomaterials* **2006**, *27*, 5561-5571.
212. Ferris, D.; Moodie, G.; Dimond, P.; Giorani, C.; Ehrlich, M.; Valentini, R. RGD-coated titanium implants stimulate increased bone formation in vivo. *Biomaterials* **1999**, *20*, 2323-2331.
213. Schneiders, W.; Reinstorf, A.; Pompe, W.; Grass, R.; Biewener, A.; Holch, M.; Zwipp, H.; Rammelt, S. Effect of modification of hydroxyapatite/collagen composites with sodium citrate, phosphoserine, phosphoserine/RGD-peptide and calcium carbonate on bone remodelling. *Bone* **2007**, *40*, 1048-1059.
214. Zhang, L.; Hemraz, U.D.; Fenniri, H.; Webster, T.J. Tuning cell adhesion on titanium with osteogenic rosette nanotubes. *Journal of biomedical materials research Part A* **2010**, *95*, 550-563.
215. Balasundaram, G.; Shimp, T.M.; Sanow, W.R.; Storey, D.M.; Kitchell, B.S.; Webster, T.J. Molecular plasma deposited peptides on anodized nanotubular titanium: an osteoblast density study. *Journal of Biomedical Materials Research Part A* **2011**, *98*, 192-200.
216. Kim, J.E.; Kim, S.H.; Jung, Y. In situ chondrogenic differentiation of bone marrow stromal cells in bioactive self-assembled peptide gels. *Journal of bioscience and bioengineering* **2015**, *120*, 91-98.
217. Chen, J.; Li, Y.; Wang, B.; Yang, J.; Heng, B.C.; Yang, Z.; Ge, Z.; Lin, J. TGF- β 1 affinity peptides incorporated within a chitosan sponge scaffold can significantly enhance cartilage regeneration. *Journal of Materials Chemistry B* **2018**, *6*, 675-687.
218. Ju, X.; Liu, X.; Zhang, Y.; Chen, X.; Chen, M.; Shen, H.; Feng, Y.; Liu, J.; Wang, M.; Shi, Q. A photo-crosslinked proteinogenic hydrogel enabling self-recruitment of endogenous TGF- β 1 for cartilage regeneration. *Smart Materials in Medicine* **2022**, *3*, 85-93.
219. Hsieh, Y.-H.; Hsieh, M.-F.; Fang, C.-H.; Jiang, C.-P.; Lin, B.; Lee, H.-M. Osteochondral regeneration induced by TGF- β loaded photo cross-linked hyaluronic acid hydrogel infiltrated in fused deposition-manufactured composite scaffold of hydroxyapatite and poly (ethylene glycol)-block-poly (ϵ -caprolactone). *Polymers* **2017**, *9*, 182.
220. Ding, X.; Gao, J.; Yu, X.; Shi, J.; Chen, J.; Yu, L.; Chen, S.; Ding, J. 3D-printed porous scaffolds of hydrogels modified with TGF- β 1 binding peptides to promote in vivo cartilage regeneration and animal gait restoration. *ACS applied materials & interfaces* **2022**, *14*, 15982-15995.
221. Burdick, J.A.; Anseth, K.S. Photoencapsulation of osteoblasts in injectable RGD-modified PEG hydrogels for bone tissue engineering. *Biomaterials* **2002**, *23*, 4315-4323.
222. Zhang, X.; Gu, J.; Zhang, Y.; Tan, Y.; Zhou, J.; Zhou, D. Immobilization of RGD peptide onto the surface of apatite-wollastonite ceramic for enhanced osteoblast adhesion and bone regeneration. *Journal of Wuhan University of Technology-Mater. Sci. Ed.* **2014**, *29*, 626-634.
223. Pan, H.; Zheng, Q.; Yang, S.; Guo, X.; Wu, B.; Zou, Z.; Duan, Z. A novel peptide-modified and gene-activated biomimetic bone matrix accelerating bone regeneration. *Journal of Biomedical Materials Research Part A* **2014**, *102*, 2864-2874.
224. Wang, C.; Yue, H.; Huang, W.; Lin, X.; Xie, X.; He, Z.; He, X.; Liu, S.; Bai, L.; Lu, B. Cryogenic 3D printing of heterogeneous scaffolds with gradient mechanical strengths and spatial delivery of osteogenic peptide/TGF- β 1 for osteochondral tissue regeneration. *Biofabrication* **2020**, *12*, 025030.

225. Zhang, S.; Zhou, X.; Liu, T.; Huang, Y.; Li, J. The effects of Peptide Mel4-coated titanium plates on infection rabbits after internal fixation of open fractures. *Archives of Orthopaedic and Trauma Surgery* **2022**, 1-6.
226. Chen, X.; Zhou, L.; Wu, D.; Huang, W.; Lin, Y.; Zhou, B.; Chen, J. The effects of titanium surfaces modified with an antimicrobial peptide GL13K by silanization on polarization, anti-inflammatory, and proinflammatory properties of macrophages. *BioMed Research International* **2020**, 2020.
227. Fischer, N.G.; Chen, X.; Astleford-Hopper, K.; He, J.; Mullikin, A.F.; Mansky, K.C.; Aparicio, C. Antimicrobial and enzyme-responsive multi-peptide surfaces for bone-anchored devices. *Materials Science and Engineering: C* **2021**, 125, 112108.
228. Hoyos-Nogues, M.; Velasco, F.; Ginebra, M.-P.; Manero, J.M.; Gil, F.J.; Mas-Moruno, C. Regenerating bone via multifunctional coatings: the blending of cell integration and bacterial inhibition properties on the surface of biomaterials. *ACS Applied Materials & Interfaces* **2017**, 9, 21618-21630.
229. Cheng, H.; Yue, K.; Kazemzadeh-Narbat, M.; Liu, Y.; Khalilpour, A.; Li, B.; Zhang, Y.S.; Annabi, N.; Khademhosseini, A. Mussel-inspired multifunctional hydrogel coating for prevention of infections and enhanced osteogenesis. *ACS applied materials & interfaces* **2017**, 9, 11428-11439.
230. Zhongxing, L.; Shaohong, W.; Jinlong, L.; Limin, Z.; Yuanzheng, W.; Haipeng, G.; Jian, C. Three-dimensional printed hydroxyapatite bone tissue engineering scaffold with antibacterial and osteogenic ability. *Journal of Biological Engineering* **2021**, 15, 1-14.
231. Liu, Z.; Yuan, X.; Liu, M.; Fernandes, G.; Zhang, Y.; Yang, S.; Ionita, C.N.; Yang, S. Antimicrobial peptide combined with BMP2-modified mesenchymal stem cells promotes calvarial repair in an osteolytic model. *Molecular Therapy* **2018**, 26, 199-207.
232. Li, N.; Bai, J.; Wang, W.; Liang, X.; Zhang, W.; Li, W.; Lu, L.; Xiao, L.; Xu, Y.; Wang, Z. Facile and versatile surface functional polyetheretherketone with enhanced bacteriostasis and osseointegrative capability for implant application. *ACS Applied Materials & Interfaces* **2021**, 13, 59731-59746.
233. Yuan, X.; Ouyang, L.; Luo, Y.; Sun, Z.; Yang, C.; Wang, J.; Liu, X.; Zhang, X. Multifunctional sulfonated polyetheretherketone coating with beta-defensin-14 for yielding durable and broad-spectrum antibacterial activity and osseointegration. *Acta Biomaterialia* **2019**, 86, 323-337.
234. Trzcińska, Z.; Bruggeman, M.; Ijkipour, H.; Hodges, N.J.; Bowen, J.; Stamboulis, A. Polydopamine linking substrate for amps: Characterisation and stability on ti6al4v. *Materials* **2020**, 13, 3714.
235. Meng, X.; Zhang, J.; Chen, J.; Nie, B.; Yue, B.; Zhang, W.; Lyu, Z.; Long, T.; Wang, Y. KR-12 coating of polyetheretherketone (PEEK) surface via polydopamine improves osteointegration and antibacterial activity in vivo. *Journal of Materials Chemistry B* **2020**, 8, 10190-10204.

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