Designer functionalised self-assembling peptide nanofibre scaffolds for cartilage tissue engineering

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Owing to the limited regenerative capacity of cartilage tissue, cartilage repair remains a challenge in clinical treatment. Tissue engineering has emerged as a promising and important approach to repair cartilage defects. It is well known that material scaffolds are regarded as a fundamental element of tissue engineering. Novel biomaterial scaffolds formed by self-assembling peptides consist of nanofibre networks highly resembling natural extracellular matrices, and their fabrication is based on the principle of molecular self-assembly. Indeed, peptide nanofibre scaffolds have obtained much progress in repairing various damaged tissues (e.g. cartilage, bone, nerve, heart and blood vessel). This review outlines the rational design of peptide nanofibre scaffolds and their potential in cartilage tissue engineering.

Introduction

Cartilage is a resilient load-bearing tissue and provides a smooth surface with low friction that can withstand and distribute high tensile stresses (Ref. 1). Articular cartilage has the capability to increase joint congruence, protect the subchondral bone from high stresses and reduce friction at the edge of long bones (Refs 2, 3). Cartilage defects have become increasingly ubiquitous in clinical medicine, and they are mainly caused by trauma, tumour removal, osteoarthritis (OA) and rheumatoid arthritis (Refs 4, 5, 6, 7, 8). For instance, patients with OA suffer from worsening pain, tenderness and mobility because of the progressive degeneration of the joint. OA can eventually lead to full-thickness focal chondral defects and represents a huge socioeconomic burden to the society (Refs 9, 10). However, cartilage tissues have very limited regenerative ability because of the lack of vascular networks, low cellularity and proliferation rate of chondrocytes, as well as the formation of protease inhibitors and growth inhibitor (Refs 11, 12, 13). Natural repair of full-thickness cartilage defects results in fibrocartilage formation with function and mechanical force inferior to the original hyaline cartilage, and further deterioration can occur (Refs 9, 10, 14). Although many clinical treatments have been developed for cartilage repair, there are still lack of effective treatments and the long-term prognosis is not good (Refs 9, 15, 16, 17).

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Tissue engineering has emerged as an interdisciplinary field merged by life sciences, physical sciences and engineering, and holds great promise in repairing various tissues or organs (Refs 18, 19, 20, 21). It is well known that tissue engineering has the ability not only to rebuild the structure of damaged tissues, but also to recover their biological functions (Refs 22, 23, 24). Enormous studies have demonstrated the capability of tissue engineering in repairing damaged tissues or organs (e.g. cartilage (Refs 9, 25), bone (Refs 9, 26, 27), nerve (Refs 18, 28), heart (Refs 29, 30) and bladder (Refs 31, 32)). Material scaffold is considered to be one of the important and key elements of cartilage tissue engineering (Ref. 9). Peptide nanofibre scaffolds are regarded as an ideal candidate material for enhancing cartilage regeneration (Refs 33, 34, 35). Their fabrication is based on the principle of molecular self-assembly, which relies on chemical complementarity and structural compatibility (Refs 18, 36). Peptide self-assembly into supramolecular architectures are supported by numerous non-covalent intermolecular interactions (e.g. hydrogen bonds, ionic interactions, electrostatic interactions, hydrophobic interactions, van der Waals forces and water-mediated hydrogen bonds) (Refs 36, 37). Although these intermolecular interactions are relatively weak in isolation, collectively they can exert strong molecular forces to initiate peptide self-assembly and improve the stability of supramolecular structures (Refs 36, 38, 39, 40).

There have been many peptides used to construct three-dimensional (3D) biomaterial scaffolds and they are grossly divided into three categories (i.e. β-sheet peptides, α-helical peptides and collagen-mimetic peptides) (Refs 18, 40, 41, 42). It is widely accepted that β-sheet peptides play a dominant role in the design and fabrication of peptide-based biomaterials (Refs 18, 41, 43). They include ionic self-complementary peptides (Refs 44, 45), peptide amphiphile (PA) (Refs 39, 46, 47), self-assembling β-hairpins peptides (Refs 48, 49), β-sheet tapes (Refs 50, 51), ABA-block copolymer (Refs 52, 53), various dipeptide and fluorenylmethoxycarbonyl (Fmoc)-conjugates (Refs 54, 55, 56). Modification with peptide epitopes (i.e. functional motifs) and controlled release of molecular signals (e.g. growth factors, cytokines and chemokines) are capable to increase the similarity of peptide nanostructures to natural extracellular matrices (ECMs), and to significantly improve the bioactivity of peptide nanofibre scaffolds for cell function and tissue regeneration (Refs 18, 41).

In the β-sheet system, self-assembly peptides have been extensively developed to form β-sheet secondary structure and 3D nanofibre scaffolds for various biomedical applications (Refs 42, 45, 57, 58). For instance, RADA16-I peptide nanofibre scaffolds are able to facilitate neurite outgrowth, heart and bone regeneration as well as wound healing (Refs 59, 60, 61, 62), whereas nanofibre scaffolds derived from KLDL12 peptides are beneficial to chondrocyte culture and cartilage regeneration (Refs 63, 64). IKVAV-PA hydrogels have the capability to inhibit nerve scar formation, and promote robust regeneration of nerve fibres (Refs 65, 66). Furthermore, peptide scaffolds formed by rP11–4 peptides and Fmoc-RGD peptides can augment the cell function of dermal fibroblasts (Refs 67, 68). This review will highlight the potential of peptide nanofibre scaffolds in cartilage tissue engineering.

Clinical treatments for cartilage repair

There have been many important treatments for cartilage defects, and they include debridement (Refs 69, 70), cell-based therapies such as autologous chondrocyte implantation (ACI) (Refs 71, 72) and matrix-induced chondrocyte implantation (MACI) (Refs 71, 73), replacement of the damaged tissues (e.g. by mosaicplasty (Ref. 74), autograft and allograft transplantation (Refs 75, 76)), as well as recruitment of mesenchymal stromal cells by microfracture (Ref. 77). Cartilage autografts are regarded as the golden standard for treating cartilage defects, but are limited by the shortage of donor grafts and the donor site morbidity (Refs 78, 79). Although other treatments provide fairly acceptable clinical results, repaired cartilage tissues have mechanical property and function inferior to natural hyaline cartilage and patients with these treatments do not have a good long-term prognosis (Refs 15, 16, 25, 80, 81, 82).

Cartilage tissue engineering has become an increasingly important approach to optimise the functional restoration of damaged tissues, and focuses on the optimal combination of material scaffolds, cells and signal molecules (Ref. 83). Material scaffolds used in cartilage tissue engineering can be grossly classified into three

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groups: (1) natural materials such as collagen (Ref. 84), gelatin (Ref. 85), fibrin (Ref. 86), alginate (Ref. 87), agarose (Ref. 88), chitosan (Ref. 89) and hyaluronan (Ref. 90); (2) synthetic materials such as polylactic acid (PLA) (Ref. 91), poly(glycolic acid) (PGA) (Ref. 2), poly(lactic-co-glycolic) acid (PLGA) (Ref. 92) and polycaprolactone (PCL) (Ref. 93); as well as (3) their composites such as PGA/fibrin (Ref. 94), collagen type II and RGD peptide-modified PLA/PLGA (Ref. 95). Natural materials have good biocompatibility and biodegradation and are able to mimic certain aspects of native ECMs. They have favourable influence on cell functions (e.g. cell proliferation, migration and differentiation) and ECMs formation (Ref. 96). However, these materials are limited by immunogenecity, difficulty in processing, pathogens transmission and relatively weak mechanical force (Ref. 15, 96). Synthetic materials have the advantage of relatively easy production as well as the ability to control dissolution and degradation (Ref. 97). However, these synthetic materials have relatively low bioactivity for cell function and tissue regeneration. Meanwhile, they may elicit inflammatory responses (Ref. 98). Thus, there is a great need to develop novel material scaffolds for cartilage tissue engineering.

Peptide-based biomaterials

Peptides are regarded as versatile building blocks for fabricating supramolecular architectures, and peptide-adopted secondary structures (e.g. β-sheet, α-helix and collagen-like triple helix) contribute favourably to the design and fabrication of self-assembling biomaterials with hierarchical 3D macromolecular architectures (e.g. synthetic membranes, multilamellar structures, amphiphilic micelles, tubules and fibrillar networks), nanoscale features and tunable physical properties (Refs 18, 36, 37, 40, 99). Peptide self-assembly is highly specific and the stability of peptide structures is reinforced by enormous noncovalent intermolecular interactions (Refs 18, 36). The interactions between adjacent peptides can be manipulated through engineering the amino acid sequences and secondary structures of peptides (Refs 37, 38). Chemical design versatility of peptides and specific secondary structures provide the feasibility to tailor the structural features of peptide scaffolds (Refs 36, 38, 41). This review would focus on β-sheet peptides-formed nanofibre scaffolds that have showed extraordinary ability to promote cartilage regeneration.

Ionic self-complementary peptides

In the early 1990s, a natural protein motif Zuotin in a yeast protein was serendipitously found to have the ability to form nanofibres and 3D nanostructure (Ref. 44). It is the first member of ionic self-complementary peptides and has the peptide sequence AEAEAKAKAEAEAKAK (i.e. EAK16-II) (Refs 44, 100). Ionic self-complementary peptides are comprised of periodic repeats of hydrophobic sides (e.g. alanine, valine, leucine, isoleucine and phenylalanine) and hydrophilic sides such as positively charged amino acid (e.g. lysine, arginine and histidine) and negatively charged amino acids (e.g. aspartic acids and glutamic acids) (Refs 18, 36, 100). The complementary ionic sides are categorized into several moduli (e.g. modulus I, II, III, IV and mixed moduli: modulus I, − + − + − + − +; modulus II, − − + + − − + +; modulus III, − − − + + +; and modulus IV, − − − − + + + +) based on the hydrophilic surfaces of the molecules (Refs 36, 100, 101). In addition, the design of charge orientation in reverse orientations can produce entirely different molecules with distinct molecular behaviours (Refs 36, 38). There have been many ionic self-complementary peptides that are under extensive studies (Table 1) (Refs 102, 103, 104, 105). During peptide self-assembly, the hydrophobic charged amino acids yield overlapping hydrophobic interactions, whereas positive and negative charges of adjacent peptides pack together through intermolecular ionic interactions in a checkerboard-like manner (Refs 100, 106). Assembling environment (e.g. ion strength, temperature, pH of the solution and denaturing agents) is found to have no significant influence on ionic self-complementary peptides-formed nanostructures (Refs 105, 107, 108). For instance, after the incubation of d-EAK16 peptides at 100°C for 4 h, the secondary structures of peptides have the propensity to undergo a transition from β-sheet to α-helix, indicating that β-sheet structure is unstable when meeting dramatically temperature change. After continuous incubation for 2 days, almost all peptides can form nanofibres (Fig. 1a) (Ref. 105). In the solution with pH value ranging from 3.7

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Table 1. The members of self-assembling ionic-complementary peptides (Refs 102, 103, 104, 105).

Peptide	Sequence (n → c)	Charge distribution	Secondary structure
KFE8-I[T]	n-KFEFKFEF-c	+ −+ −	β
KFE8-I	n-FKFEFKFE-c	+ −+ −	β
EFK8-I	n-FEFKFEFK-c	−+− +	β
KFE12-I	n-FKFEFKFEFKFE-c	+ −+ − +−	β
KIE12-I	n-IKIEIKIEIKIE-c	+ −+ − +−	β
KVE12-I	n-VKVEVKVEVKVE-c	+ −+ − +−	β
KLD12-I	n-KLDLKLDLKLDL-c	+ −+ − +−	β
KLE12-I	n-KLELKLELKLEL-c	+ −+ − +−	β
EFK12-I	n-FEFKFEFKFEFK-c	−+ − +− +	β
RADA16-I	n-RADARADARADARADA-c	+ −+ − +− + −	β
RAEA16-I	n-RAEARAEARAEARAEA-c	+ −+ − +− + −	β
KADA16-I	n-KADAKADAKADAKADA-c	+ −+ − +− + −	β
KFE16-I	n-FKFEFKFEFKFEFKFE-c	+ −+ − +− + −	β
EAK16-I	n-AEAKAEAKAEAKAEAK-c	−+ − +− +− +	β
ELK8-II	n-LELELKLK-c	− −+ +	β
RAD16-II	n-RARADADARARADADA-c	++− −+ + −−	β
EAH16-II	n-AEAEAHAHAEAEAHAH-c	− −+ + −− + +	β
EFK16-II	n-FEFEFKFKFEFEFKFK-c	− −+ + −− + +	β
ELK16-II	n-LELELKLKLELELKLK-c	− −+ + −− + +	β
EAK16-II	n-AEAEAKAKAEAEAKAK-c	− −+ + −− + +	β
KAE16-IV	n-KAKAKAKAEAEAEAEA-c	++ + +− −− −	β
RAD16-IV	n-RARARARADADADADA-c	++ + +− −− −	β
EAK16-IV	n-AEAEAEAEAKAKAKAK-c	−−− −+ + ++	β
D-EAK16	n-$(A^DE^DA^DE^DA^DK^DA^DK^D)_2$-c	− −+ + −− + +	β

to 10.6, β-sheet structures formed by d-EAK16 peptides are relatively stable, and only in the solution with pH value below 1.0 and above 12.8, their stability can be reduced (Fig. 1b) (Ref. 105). Some denaturing agents (e.g. 1% SDS, 8.1 M urea and 7.1 M Guanidine.HCl) are used as an interference to peptide self-assembly, but no notable changes of d-EAK16 peptide-formed structures are observed from atomic force microscopy (AFM) images (Fig. 1c) (Ref. 105). Although many factors (e.g. peptide sequences, secondary structures, assembling environment and assembly kinetics) have been identified to have some impact on peptide self-assembly, the detailed mechanisms mediating peptide self-assembly into nanofibre scaffolds are still not clear (Refs 18, 36, 37, 40, 106). Additionally, it is found that proteases can degrade L-form peptide bonds but cannot degrade D-form peptide bonds, suggesting that D-amino acids may

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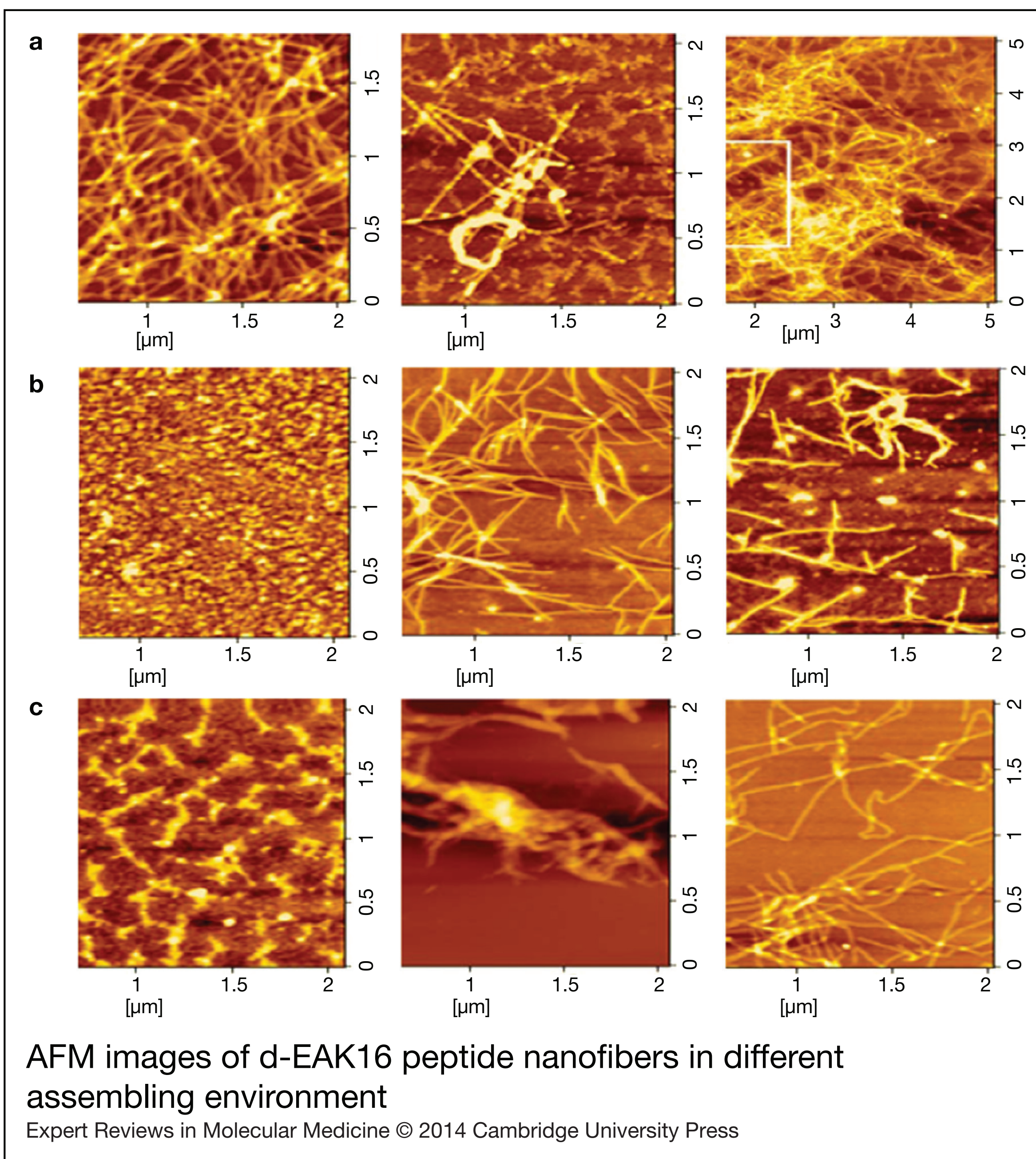

Figure 1. AFM images of d-EAK16 peptide nanofibres in different assembling environment: (a) d-EAK16 peptide solution is incubated at 25°C for 4 h and then PBS is added for self-assembling overnight (left). d-EAK16 peptide solution is incubated at 100°C for 4 h and PBS is added for self-assembling overnight (middle). d-EAK16 peptide solution is incubated at 100°C for 4 h and PBS is added to stimulate self-assembly for two nights (right). (b) d-EAK16 peptides (100 μM) are displayed under different pH conditions. At pH 1, globular structures are formed (left). At pH 7, nanofibres are formed (middle). At pH 10.6, both globular structures and nanofibres are formed (right). (c) d-EAK16 peptides (1 mg/ml, 0.1%) are incubated with different denaturation agents: 1% SDS (left), 8.1 M urea (middle) and 7.1 M Guanidine.HCl (right) (Ref. 105). Adapted and reprinted with permission from (Ref. 105).

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contribute to the better stability of peptide bonds than L-amino acids (Refs 44, 105). Nanofibre scaffolds formed by D-form peptide or even the combination of L-form and D-form peptides are likely to have some special biomedical applications (Ref. 18).

Peptide amphiphile

The chemical structure of a representative PA molecule has four key structural units including the hydrophobic domain (e.g. a long alkyl tail), a short peptide sequence capable to form intermolecular hydrogen bonding, charged amino acids for the design of pH and salt-responsive nanostructures, as well as the hydrophobic alkyl tail (e.g. peptide epitopes) for the interactions with cells or proteins (Fig. 2a) (Refs 41, 43, 46). The peptide sequences immediately adjacent to the hydrophobic segment benefit to form intermolecular hydrogen bonding (Refs 39, 46). For the assembly of PAs in water, there are three major energy contributions: hydrophobic interactions of the alkyl tails, hydrogen bonding among the middle peptide segments and electrostatic repulsions between the charged amino acids (Refs 41, 43). Their delicate balance determines the size, shape and interfacial curvature of final assemblies. The sheet-like structure of a group of PAs rather than the tapered shape of a single PA can be assembled together through intermolecular hydrogen bonding and subsequently form nanofibres as well as 3D biomaterial scaffolds (Refs 41, 109). Functional modification of PAs using peptide epitopes (e.g. RGD and IKVAV) is beneficial to cell behaviours (e.g. adhesion, proliferation and differentiation) (Refs 42, 110, 111). These nanofibre scaffolds can act as carriers for signal molecules and hydrophobic drugs crucial for cell function and tissue regeneration (Ref. 41).

Other β-sheet peptides

In one of the β-sheet tapes, Q11 peptides are found to have the ability to form nanofibre hydrogels (Fig. 2b) (Ref. 50). They can also be modified with peptide epitopes that are beneficial to cell differentiation and attachment (Ref. 112). Dipeptides modified with an N-terminal Fmoc moiety are developed to form nanofibres and hydrogels. Hydrophobic interaction, π–π stacking effects and intermolecular β-sheet hydrogen bonds facilitate the supramolecular association and substantially improve structural stability (Ref. 54). For instance, fluorenylmethoxycarbonyl-diphenylalanine (Fmoc-FF) can yield stable hydrogels in physiological condition and show extraordinary cytocompatibility with chondrocytes. Combining Fmoc-FF dipeptide with Fmoc-modified amino acids (e.g. lysine, glutamic acid, arginine and serine) is intended to optimise gel stiffness and possibly increase bioactivity (Fig. 2c) (Ref. 113). In the β-sheet system, there also have been other peptide-based nanofibre scaffolds derived from self-assembling β-hairpins peptides and ABA-block copolymer (Refs 48, 52).

Rational design of peptide nanofibre scaffolds resembling ECMs

Natural ECMs

Cartilage ECMs are comprised of various collagens, proteoglycans and glycosaminoglycans (GAGs) in which multiple bioactive factors (e.g. growth factors and functional peptides) are incorporated (Refs 9, 114). Natural tissue regeneration is mediated by highly complex temporal and spatial coordination of diverse cell–matrix and cell–cell interactions which are regulated by: (1) insoluble hydrated macromolecules (e.g. collagens, elastin, laminin and fibronectin), (2) soluble macromolecules (e.g. growth factors, chemokines and cytokines) and (3) proteins on the surfaces of neighbouring cells (Refs 19, 20, 115). In addition, an external stimulus (e.g. biomechanical triggers) also has an influence on the reciprocal interaction between cells and ECMs (Ref. 116). The ultimate decision of cell function and ECM production is a coordinated response of cells to these ECM effectors (Ref. 19). It is very difficult and important to manipulate the right quantity of molecular signals for corresponding cells to elicit cell function at the right time (Refs 117, 118).

Increasing the similarity to natural ECMs

Rather than directly reconstructing tissue or organs ex vivo, an emerging design philosophy for tissue engineering scaffolds is to develop smart biomaterials to induce the body's innate powers of organisation and self-repair (Ref. 20). It is very important to obtain the symbiosis of material scaffolds, cells and signal molecules (Refs 18, 19). The design and fabrication of peptide nanofibre scaffolds for biomedical applications should focus on mimicking the microstructure and regulatory mechanisms of

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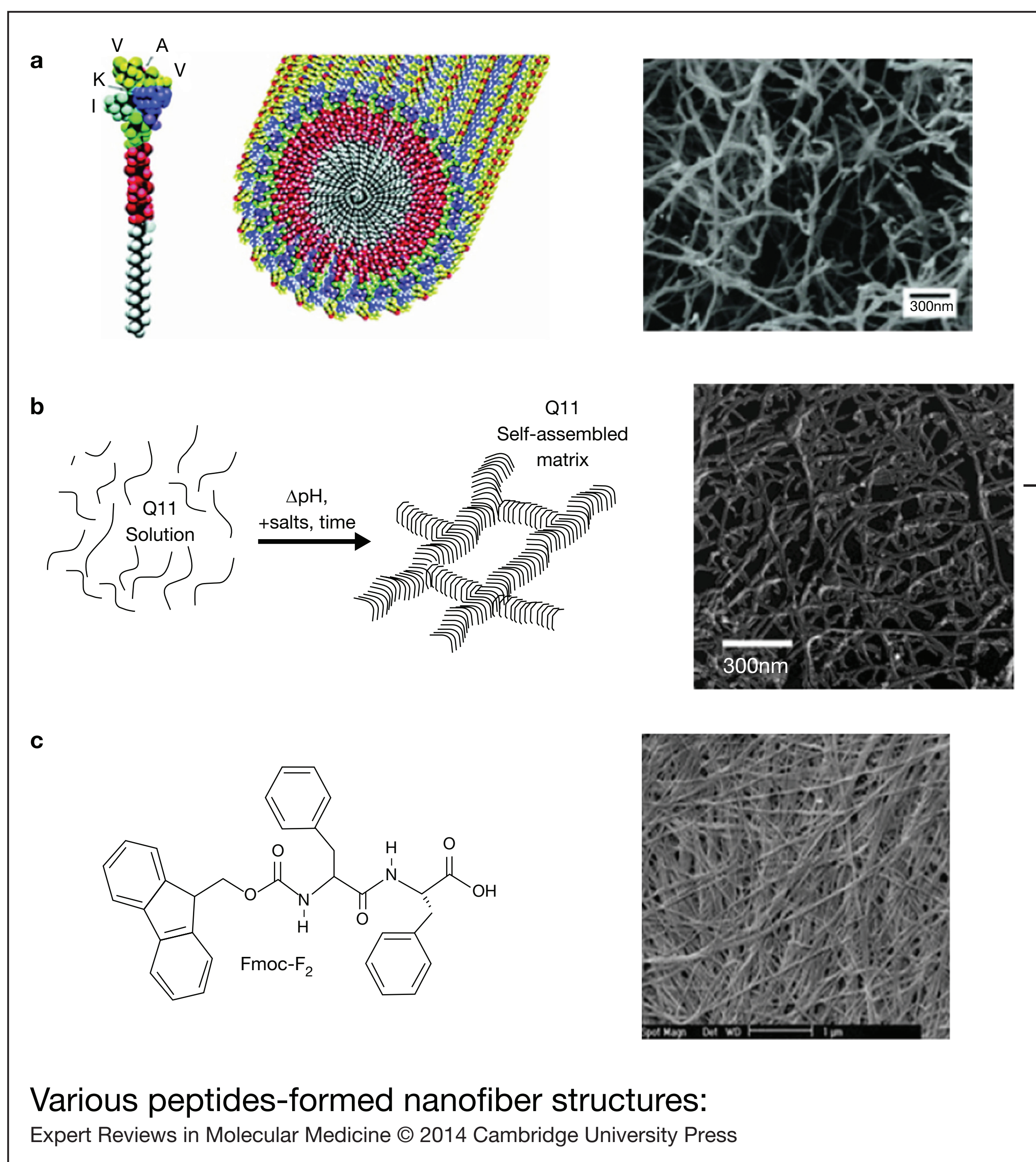

Figure 2. Various peptides-formed nanofibre structures: (a) molecular model of an IKVAV-containing PA, their self-assembly into nanofibres, as well as scanning electron microscopy (SEM) image of IKVAV nanofibres after adding cell media (DMEM) to PA aqueous solution (Ref. 41). (b) Q11 peptides are stimulated to self-assemble by the addition of salts, pH change, or the passage of time, and consequently they result in self-assembled matrix. Quick-freeze deep etch (QFDE) TEM images shows that Q11 peptides are assembled into a highly entangled network with fibrils of ~20 nm in diameter and ~100 nm between entanglement points (Ref. 50). (c) Chemical structure Fmoc-FF dipeptide and Cryo-SEM image of Fmoc-FF/K (1:1) nanofibrous hydrogel (Ref. 113). Adapted and reprinted with permission from (Refs 41, 50, 113).

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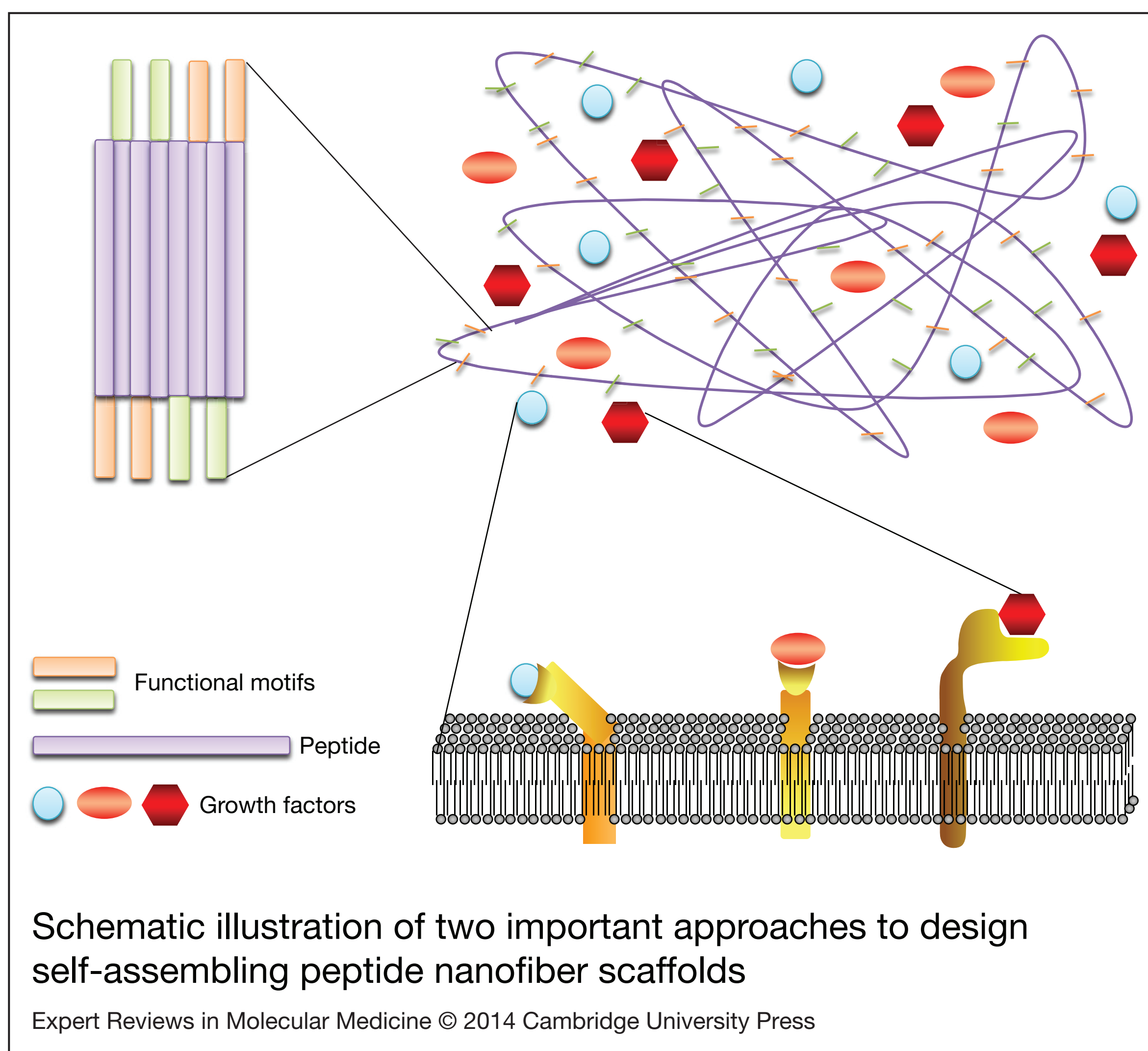

Figure 3. Schematic illustration of two important approaches to design self-assembling peptide nanofibre scaffolds: there have been many self-assembling peptide sequences that can be modified with functional motifs (e.g. RGD and IKVAV). These self-assembling peptides have the ability to form stable 3D nanofibre structures with functional motifs. The density of these motifs can be changed through mixing self-assembling peptides and peptides with functional motifs in different ratios. In addition, it is feasible to store, retain and release various signal molecules (e.g. growth factors) within such 3D nanofibre scaffolds. These released growth factors and functional motifs can significantly induce cell function and tissue regeneration via binding to their corresponding receptors.

natural ECMs. The diameter of nanofibres and pore size of peptide nanofibre scaffolds are at nanometer scale (Refs 18, 41, 43). For instance, ionic self-complementary peptide-formed scaffolds have nanofibres with ~10–20 nm in diameter and pore size ranging from ~5 to 200 nm (Refs 23, 36). These nanofibre networks and pore sizes are analogous to those found in natural ECMs, and they have favourable influence on cell infiltration and dwell, the delivery of oxygen and soluble signal molecules, as well as waste product removal (Refs 108, 119, 120). Furthermore, stable hydrogels can be formed and contain extremely high water content, more than 99% in water (5–10 mg/ml, w/v) (Refs 101, 107).

Two significant approaches to increase the natural ECM mimicking of peptide nanofibre scaffolds are highlighted: (1) modification with functional motifs and (2) controlled release of

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molecular signals (Fig. 3) (Refs 18, 42). There have been many functional motifs (e.g. RGD (Ref. 121), IKVAV (Ref. 122) and YIGSR (Ref. 123)) that are developed to modify biomaterial scaffolds. The tripeptide sequence RGD found in fibronectin and other ECM proteins can facilitate cell differentiation and migration through binding to α5β1 integrin receptor (Ref. 124). One study reveals that lower RGD concentrations are found to assist in the maintenance of chondrocyte number and phenotype, as well as the increase in ECM contents compared with higher RGD concentrations (Ref. 125). In addition, peptide PHSRNG6RGD can be fabricated through combining peptide RGD and PHSRN with the aim of increasing the similarity to functional structures of fibronectin, and result in significantly increased cell binding (Ref. 126). IKVAV sequences found in laminin are able to reinforce cell adhesion, migration and angiogenesis (Ref. 18). For instance, peptide RADA16 solution and peptide RADA16–IKVAV solution are combined to form IKVAVmx hydrogel scaffolds for culturing neural stem cells, leading to substantially improved cellular proliferation, differentiation and migration when compared with pure RADA16 hydrogels (Ref. 127).

In many cases, only very tiny quantities of signal molecules are required to elicit biological response, and some cellular processes demand several signalling pathways mediated by many signal molecules (Refs 128, 129). Controlled release of signal molecules within peptide nanofibre scaffolds is both feasible and important to mediate cell–cell and cell–matrix interactions, and significantly promote cell function and tissue regeneration (Refs 19, 57, 58, 130, 131, 132). For instance, RADA16-I peptide nanofibre scaffolds can serve as good substrates to release various functional proteins, e.g. lysozyme, trypsin inhibitor, BSA, IgG, basic-fibroblast growth factor (βFGF), vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF), and these released functional proteins can maintain their original protein conformation and functionality based on the secondary and tertiary structure analyses and biological assays (Refs 120, 132). It is found that physical hindrances can prevent proteins mobility, and interactions between proteins and nanofibres can be affected by charges (Ref. 132). In vivo studies of animal model, the released bone morphogenetic protein 2 (BMP2) from self-assembled PA nanofibre scaffolds notably result in homogeneous ectopic bone formation in the back subcutis of rats (Ref. 133), while the released bFGF from PA nanofibre hydrogels leads to remarkable angiogenesis in the subcutaneous tissue of mice (Ref. 110). In addition, the local concentration of growth factors can be increased via the electrostatic interactions with heparan sulphate proteoglycans. There is possibility to manipulate the concentration of growth factors through modifying material scaffolds to mimic the heparan sulphate-binding groups (Refs 132, 134). For example, modifying an alginate hydrogel through sulphating the uronic acids in the saccharide backbone can be used to mimic the heparin/heparan sulphate-binding groups. Sustained release of angiogenic and pro-survival factors within these modified hydrogels significantly increase the capability to promote pre-vascularisation of engineered cardiac patches and repair infarcted heart (Refs 134, 135).

Cartilage regeneration using peptide nanofibre scaffolds

Peptide nanofibre scaffolds are formed by natural amino acids, and have the properties of biological self-recognition, good biocompatibility as well as nontoxic degradation products (Ref. 36). Their microstructures highly mimic the natural ECM and have appropriate porosity for cell infiltration and growth (Refs 36, 41). In addition, modification with functional motifs and controlled release of molecular signals have been under extensive studies to increase the similarity of peptide nanofibre scaffolds to the microstructure and regulatory mechanisms of natural ECMs (Refs 18, 38, 40, 41). This review would focus on the capability of peptide nanofibre scaffolds to induce cartilage repair from the aspects of cell culture in vitro and tissue regeneration in vivo.

In vitro cell culture

Many peptide nanofibre scaffolds have demonstrated the ability to induce cellular activities (e.g. proliferation, differentiation, adhesion and migration) as well as ECM production by cell culture tests in vitro (Refs 63, 64, 113). FEFEFKFK peptides-formed nanofibre scaffolds are used to culture chondrocytes, resulting in good cellular viability and proliferation, cell morphology retention as well

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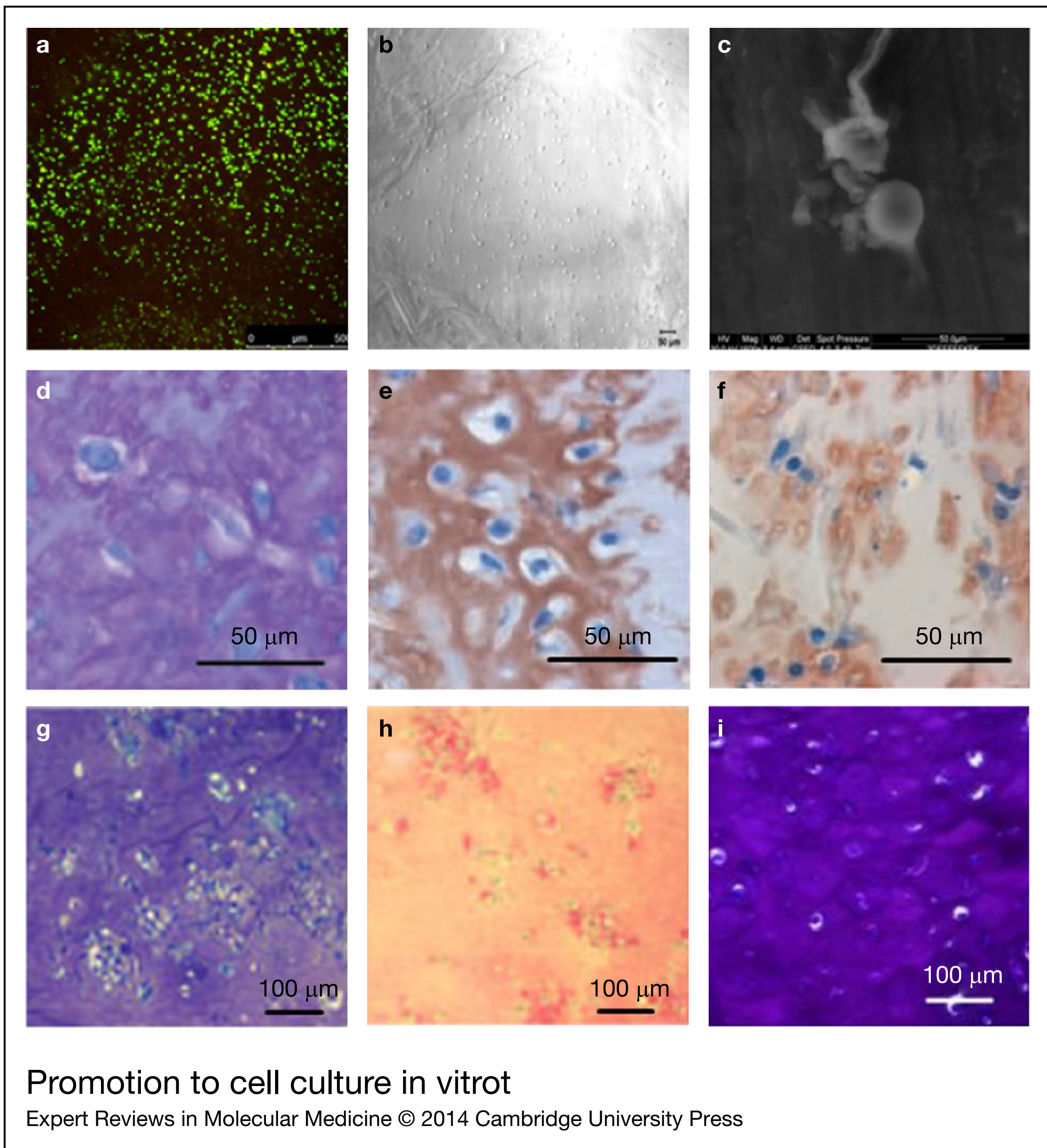

Figure 4. Promotion to cell culture in vitro: chondrocytes seeded on FEFEFKFK peptide nanofiber scaffolds contribute to good cell viability as demonstrated by (a) confocal microscopy *z*-stack image viewed along the *z*-axis (viable cells in green and the nuclei of dead cells in red) and cell morphology retention as demonstrated by (b) optical microscopy image showing the classic rounded morphology of chondrocytes in the gel matrix after 25 days culture and by (c) environmental scanning electron microscopy (ESEM) micrograph displaying a single-cell attached to the gel (Ref. 136). BMSCs cultured in RAD16-I peptide scaffolds result in extensive ECM production, as evidenced by (d) toluidine blue staining for sulphated GAG, immunohistochemistry images of (e) collagen type II and (f) type I (Ref. 33). Sustained release of TGF-β1 from KLDL12 peptide hydrogels comprising BM-MSCs is beneficial to the extensive accumulation of (g) proteoglycan identified by toluidine blue staining and (h) type II collagen identified by immunohistochemical staining (Ref. 34). (i) Chondrocyte-seeded KLDL12 peptide hydrogels substantially facilitate proteoglycan synthesis as showed by toluidine blue staining after 39 days of alternate day dynamic compression (Ref. 144). Adapted and reprinted with permission from (Refs 33, 34, 136, 144).

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as type II collagen deposition (Fig. 4a–c) (Ref. 136). Likewise, nanofibre scaffolds derived from KLDL12 and RADA16-I peptides are beneficial to culture chondrocytes and the formation of cartilage-like ECMs enriched in GAG, proteoglycans and type II collagen (Refs 63, 64). Bone marrow stromal cells (BMSCs) cultured in RAD16-I peptide hydrogels lead to the formation of sulphated GAG, type II and type I collagens (Fig. 4d–f) (Ref. 33). In addition, Fmoc-FF/S and Fmoc-FF/D hydrogels can be used to culture bovine chondrocytes, demonstrating good cell function and morphology retention (Ref. 113).

Controlled release of growth factors has been widely used for cell culture within peptide nanofibre scaffolds. For instance, KLDL12 peptide hydrogels can serve as the substrate to incorporate and release transforming growth factor β1 (TGF-β1). At day 21, cumulative release of TGF-β1 from peptide hydrogels is 32–44% as opposed to 62% of released TGF-β1 from peptide hydrogels with encapsulated BMSCs, and it is possibly associated with cell-mediated TGF-β1 degradation. Sustained release of TGF-β1 is revealed to stimulate chondrogenesis of young equine BMSCs (Ref. 137). Furthermore, KLDL12 peptide hydrogels are used to seed bone marrow mesenchymal stem cells (BM-MSCs) and the released TGF-β1 from peptide hydrogels can significantly increase cell function, as well as the synthesis of proteoglycan and type II collagen (Fig. 4g and h) (Ref. 34). Additionally, it is well known that dexamethasone (Dex) has pro-anabolic and anticatabolic effects on cartilage tissue engineering. However, in one study, RADA16 peptide hydrogels comprising TGF-β1 and Dex are utilised to culture young bovine and adult human BMSCs. The results demonstrate that the released Dex has the capability to reduce aggrecanase activity within peptide hydrogels for both young bovine and adult human BMSCs (Ref. 138).

Various types of cells have been studied to serve as cell source and result in different ECM production within peptide nanofibre scaffolds. BMSCs-incorporated KLDL12 peptide hydrogels lead to form cartilage-like neotissue with longer core protein and chondroitin sulphate chains, as well as higher mechanical stiffness than that produced by chondrocytes (Ref. 139). Compared to MSCs as a cell source, chondrocytes can produce ECMs with superior mechanical properties when using RADA16-I peptide hydrogels for cell culture (Ref. 140). In addition, for identifying the influence of GAG on chondrogenic differentiation, sulphonate, carboxylate and hydroxyl groups are incorporated on self-assembled peptide nanofibres. These functional peptide nanofibre scaffolds contribute favourably to rapid aggregation of TDC5 cells in the insulin-free medium, cartilage-like nodules formation, sulphated GAGs deposition, as well as significant gene expressions of type II collagen and aggrecan indicative of chondrogenic differentiation (Ref. 141).

Culturing mouse embryonic fibroblasts (MEFs) within peptide nanofibre hydrogels is affected by different elastic modulus values. At low elastic modulus values (approximately 0.1 kPa), both chondrogenic inductor BMP4 and its antagonist Noggin are detected, while at higher elastic modulus values (approximately 5 kPa), Noggin rather than BMP4 is detected, resulting in the inhibition of chondrogenesis. This study reveals that mechanical stimulus has important influence on cell function (Ref. 142). In another study, human dermal fibroblasts are cultured within self-assembling peptide hydrogels with standard chondrogenic medium. During the first day of culture, the 3D constructs undergoes a substantial contraction process and consequently form a small compact structure, resulting in a chondrocyte-like construct based on the elevated expression of GAG, proteoglycan aggrecan and type II collagen (Ref. 143). Furthermore, dynamic compression is found to significantly increase proteoglycan synthesis within chondrocyte-seeded KLDL12 peptide hydrogels (Fig. 4i) (Ref. 144). It is very important to control mechanical stimulus for chondrogenesis and ECM production, and much effort is needed to elucidate the mechanisms regarding the influence of mechanical stimulus on chondrogenesis.

In vivo tissue regeneration

Controlled release of growth factors from peptide nanofibre scaffolds has been used in vivo experiments. RADA16-I peptide hydrogels containing chondrocytes and TGF-β3 are transplanted into the cartilage defects of bovine model, resulting in extensive synthesis of GAG and type-II collagen, as well as good integration with native cartilage tissue and the formation of mechanically stable interface (Fig. 5a and b) (Ref. 145). Chondrogenic factors (i.e. TGF-β1,

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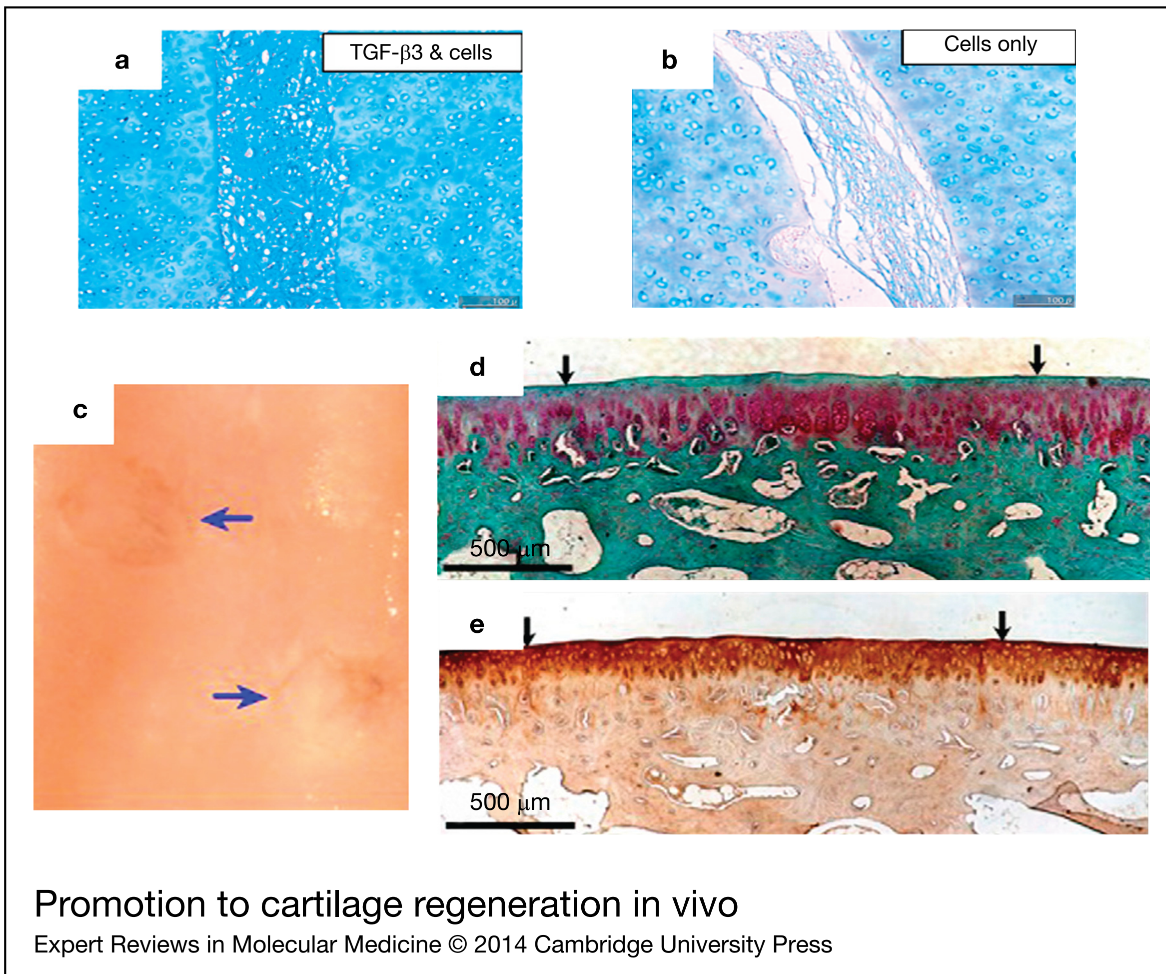

Figure 5. Promotion to cartilage regeneration in vivo: Alcian blue–eosin stained sections of the interface between the inner core and outer ring articular cartilage components at culture day 21, (a) RADA16-I hydrogel containing both TGF-β3 and chondrocytes showing robust cartilage formation in intimate contact with the native cartilage components compared to the treatment of (b) hydrogel-containing chondrocytes only (Ref. 145). Articular cartilage defects after 12 weeks postop treated with 10%TGFBPA + 100 ng/ml TGF-β1 (100TGF), showed by macroscopic views (c), histological evaluation of sample sections: (d) safranin-O staining for GAGs and (e) type II collagen staining (Ref. 35). Adapted and reprinted with permission from (Refs 35, 145).

insulin-like growth factor-1 (IGF-1) and Dex) are combined with KLDL12 peptide hydrogels to treat the full-thickness and critically sized defects of rabbit cartilage, contributing to significant formation of aggrecan and type II collagen (Ref. 146). In addition, TGF-binding PAs (TGFBPA: HSNGLPLGGGSEEEAAAVVV(K)-$CO(CH_2)_{10}CH_3$) are designed with binding epitopes to TGF-β1 and can effectively reduce the passive release of TGF-β1. In vitro experiments reveal that these peptide scaffolds comprising TGF-β1 are capable to induce the chondrogenic differentiation of human MSCs. TGF-binding PA nanofibre scaffolds comprising TGF-β1 can substantially promote the regeneration of articular cartilage in the full-thickness chondral defects treated with microfracture in the trochlea of adult rabbits in the presence of bone marrow MSCs, indicating the importance of growth factor release and functional modification within peptide nanofibre scaffolds for cartilage repair (Fig. 5c–e) (Ref. 35).

Conclusion and future prospective

Self-assembling peptide nanofibre scaffolds have become increasingly important biomaterials for

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cartilage tissue engineering. Their nanofibre networks highly mimic natural ECMs and these similarities can be increased by modification with functional motifs and controlled release of signal molecules. However, the mechanical force of peptide nanofibre scaffolds is relatively weak and it is very difficult to use such biomaterial scaffolds to repair the defects of loading-bearing cartilages.

It is generally accepted that the design of synthetic biomaterial scaffolds should aim to resemble the microstructures and regulatory mechanisms of natural ECMs for the purpose of stimulating the best regenerative ability of damaged tissues or organs. It is very important but difficult to modulate cell behaviours (e.g. proliferation, differentiation and migration) within peptide nanofibre scaffolds because these regulatory mechanisms in natural ECMs are very complicated and hard to manipulate. The design of biomaterial scaffolds mimicking natural ECMs may significantly increase the possibility of controlling cell functions.

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Table

Table 1. The members of self-assembling ionic-complementary peptides (Refs 102, 103, 104, 105)..

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