Chemistry and engineering of brush type polymers

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Historical Perspective

Chemistry and engineering of brush type polymers: Perspective towards tissue engineering

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ABSTRACT

In tissue engineering, it is imperative to control the behaviour of cells/stem cells, such as adhesion, proliferation, propagation, motility, and differentiation for tissue regeneration. Surfaces that allow cells to behave in this way are critical as support materials in tissue engineering. Among these surfaces, brush-type polymers have an important potential for tissue engineering and biomedical applications. Brush structure and length, end groups, bonding densities, hydrophilicity, surface energy, structural flexibility, thermal stability, surface chemical reactivity, rheological and tribological properties, electron and energy transfer ability, cell binding and absorption abilities for various biological molecules of brush-type polymers were increased its importance in tissue engineering applications. In addition, thanks to these functional properties and adjustable surface properties, brush type polymers are used in different high-tech applications such as electronics, sensors, anti-fouling, catalysis, purification and energy *etc.* This review comprehensively highlights the use of brush-type polymers in tissue engineering applications. Considering the superior properties of brush-type polymer structures, it is believed that in the future, it will be an effective tool in structure designs containing many different biomolecules (enzymes, proteins, *etc.*) in the field of tissue engineering.

1. Introduction

Tissue engineering aims to create new functional tissue *in vitro* or *in vivo*. In tissue engineering, substrates are needed in which the cells/stem cells required for tissue regeneration will adhere, proliferate, spread, and control their motility and differentiation [1,2].

Brush-type polymers are among the essential substrates used in tissue engineering. Brush type polymers; are structures in which another polymer chain is bound in a specific order as a side group on a polymer chain [3]. Polymer brush structures are of three types depending on the grafting density and molecular weight increase. These brush structures are low density, high density, and copolymeric brushes [4–7]. In addition to these existing brush types, there are intelligent brush type polymers in the literature whose surface properties can change with external stimuli due to the warning-response feature of the surface brush structure [8,9]. The basic properties of polymer brushes are affected by many factors. In particular, the functional properties of the brush-type polymers depend on the main chain structure, the end group of the brush polymer, the polymeric brush length, the polymeric brush density, and the molecular weight of the brush-type polymer. In addition, the branching in the brush polymer and the density of this branching also significantly change the properties of the polymer. These structures are shown in Fig. 1.

Fig. 1 shows polymer structures with brushes of different chemical structures. As the brush structure changes in these structures, the physical properties of the polymer change. Another critical factor affecting the physical properties of brush-type polymers is the dissolving power of the solvent system. The brush structure is elongated linearly, especially in suitable solvents. In weak solvents, the brush clumps towards the surface. Smart polymeric surfaces can be obtained easily using this brush structure's interaction with the solvent. As a result of the brush structure being hydrophilic or hydrophobic, the brush

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morphology changes with the solvent effect, the presence of different ions, or the change of electrical potential. By adjusting this morphology that changes significantly in these structures, structures that can be used in controlled drug release systems, controlled surface hydrophilicity, and self-cleaning surface applications can be prepared.

In particular, such smart surfaces with warning-response properties can be used in drug release systems, self-cleaning surfaces, controlled optical surfaces, chemoresponsive surfaces, and some antibacterial surfaces. The release of the drug-induced brush structure, which is trapped inside the brush structures clustered on the surface, especially in a weak solvent, by opening the brush structure on the applied surface constitutes a strong potential for controlled release systems.

When we look at the literature, we see that poly[2-(methacryloxy) ethyl dimethyl-(3-sulfopropyl] ammonium hydroxide (PMEDSAH) [10,11], poly(OEGMA-*co*-HEMA) [12], poly(acrylic acid) (PAA) [13], poly(*N*-isopropyl acrylamide) (PNIPAM) [14], block copolymer brushes (pluronic F-127: PF127) [15], poly[oligo (ethylene glycol) methacrylate] (POEGMA) [16–20] and anti-fouling PEG polymer brush type [21] polymers. Depending on the brush structure, the surface functionality and surface areas of the polymers vary significantly [22–25]. Brush-type polymer structures have basic advantages such as solubility, processability, and controllability of Tg value. In addition to these advantages, these of polymers have easy manufacturability, controllability of the softness on the surfaces, good surface energy and high surface area. Due to these structural and functional properties, brush type polymers are used for different high technological applications (electronics, sensors, anti-fouling, catalysis, purification, energy, *etc.*), as shown in Fig. 2 [26,27]. For example, polymer brush structures can be used to prepare column fillers or selective membranes to reduce biological contamination and remove dyes, heavy metals, or toxic chemicals in wastewater [26–29].

Brush-type polymers use the property of changing the surface structure to prevent biofouling (protein absorption, bacterial adhesion, toxic chemical accumulation, *etc.*) that may occur on the surface. Side groups attached to the surface change with different external stimuli, preventing proteins, bacteria, or toxic chemicals from being adsorbed to the surface. There is a physical repulsion on such surfaces.

Brush-type polymer structures are used to adjust the surface hydrophilicity. By changing the brush-type polymer structure, the liquid contact angle value of the surface can also be changed [30,31]. It is frequently encountered in tissue engineering, stem cell biology, drug delivery systems, and regenerative medicine applications. The fact that

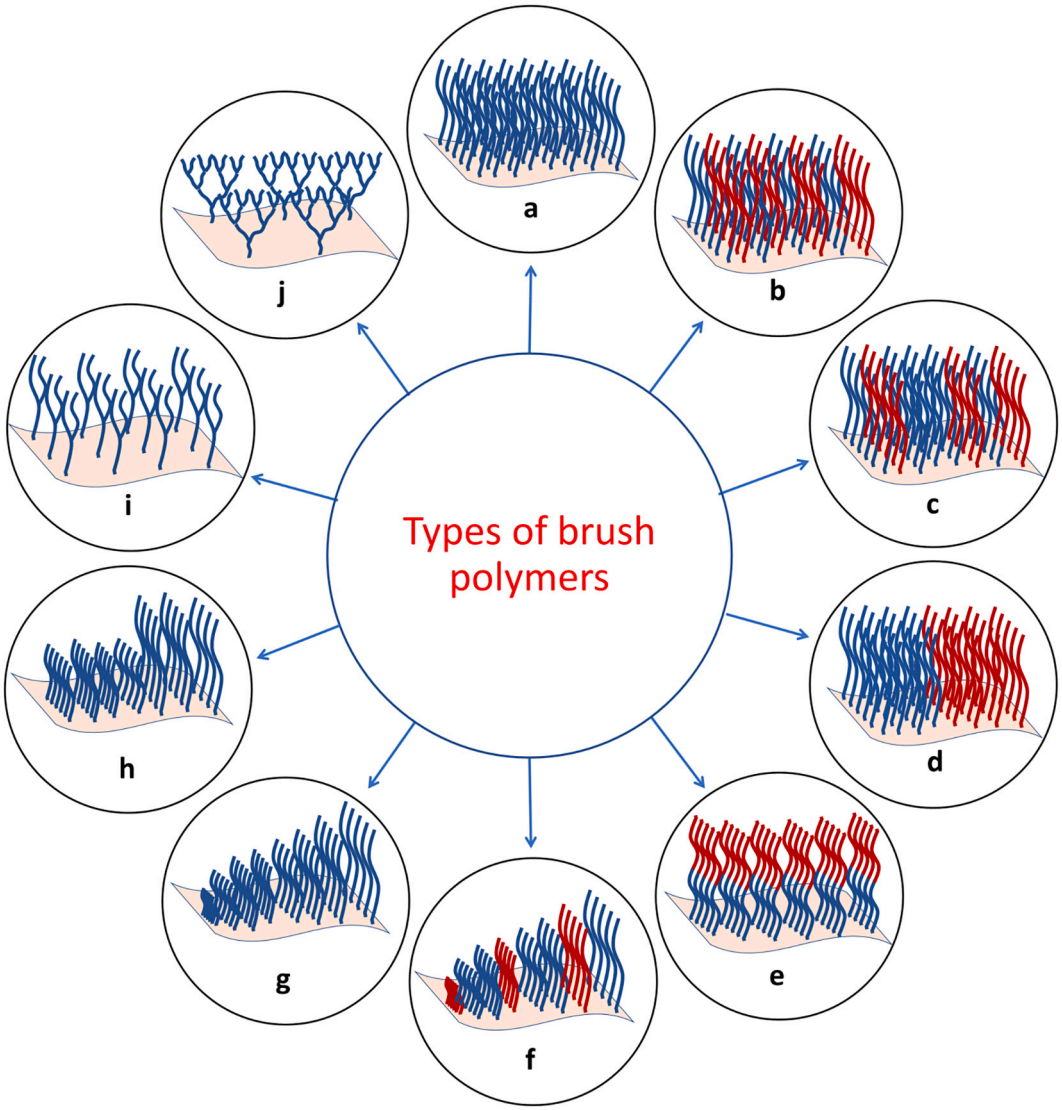

Fig. 1. Different brush-type polymer structures (a: brush type homopolymer, b: ordered mixed brush, c: disordered mixed brush, d: block mixed brushes, e: block copolymer brush, f; gradient mixed brush, g: gradient polymer brush, h: polymer brush with two brush lengths, i: heavily branched brushes, j: brushes with dendrimer structure).

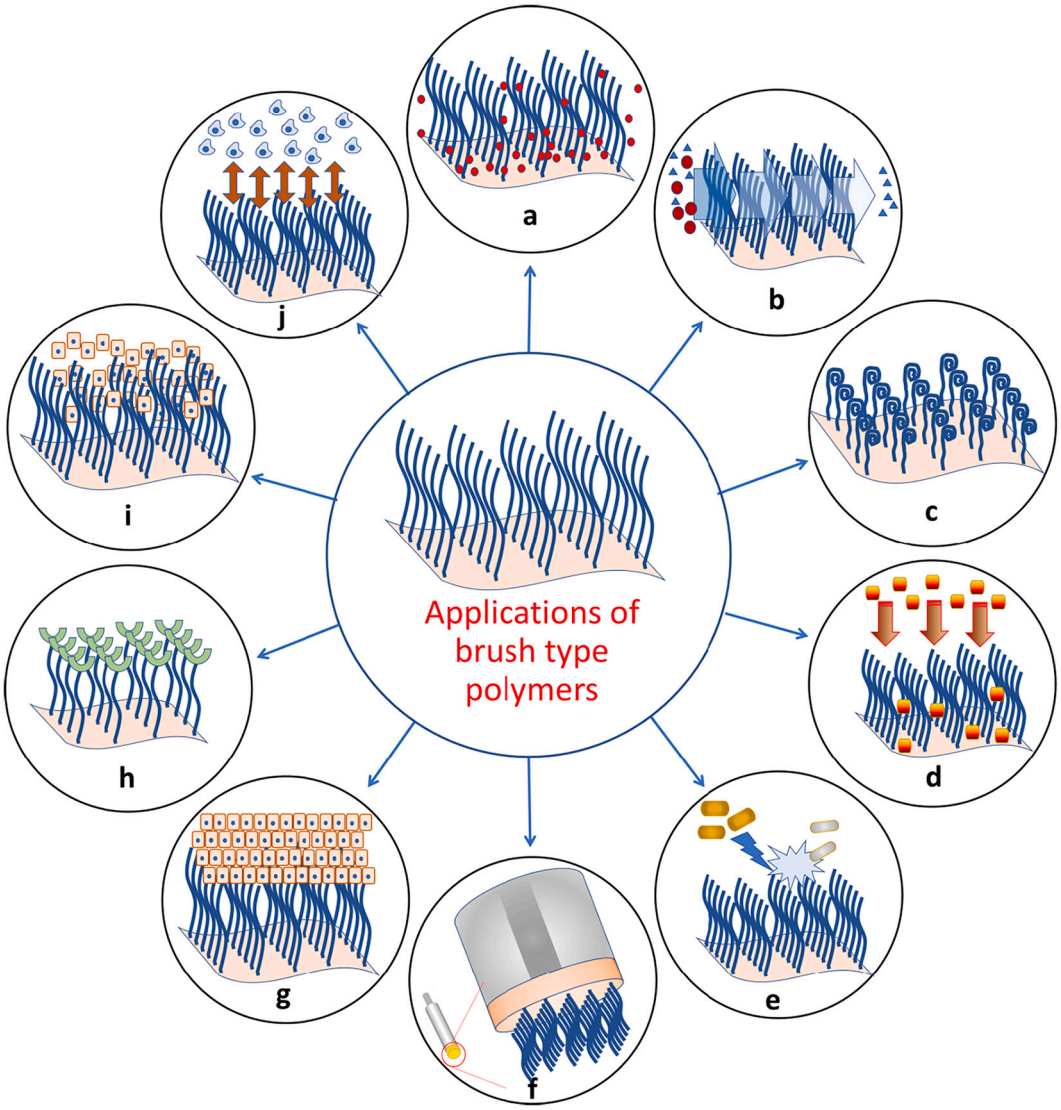

Fig. 2. Biomedical applications of brush-type polymers (a; drug delivery systems, b; membrane applications, c; smart membrane and surface applications, d; biosorption, e; antibacterial surfaces, f; biosensor applications, g; cell adhesive surfaces, h; biocompatible coatings, i; tissue engineering applications and j; antifouling surfaces).

brush-type polymer structures have distinct and regular spaces between polymeric chains is of great importance in creating tissue scaffolding and controlled drug release systems. Especially in tissue engineering, brush-type polymers give a new function by binding various molecules to substrate surfaces and result in unique interfaces similar to the microstructure of the extracellular matrix (ECM), which plays a vital role in cellular adhesion formation and proliferation. In addition, it attracts special attention in tissue engineering due to the covalent bonding

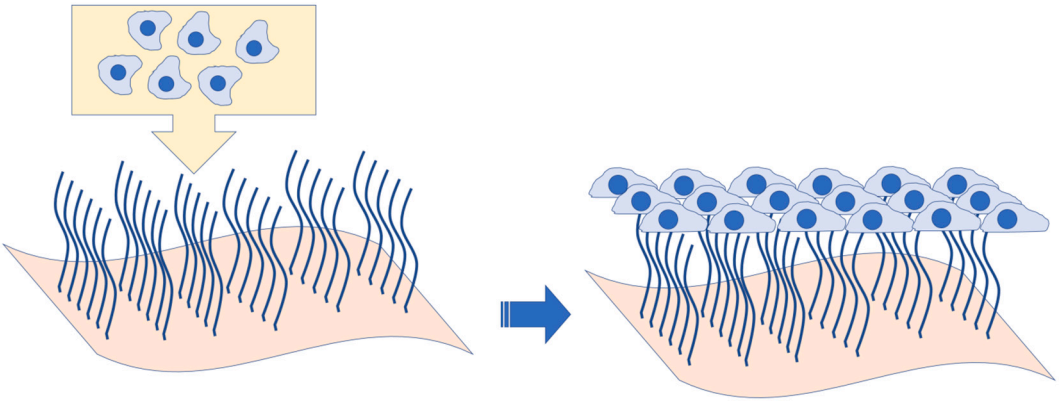

Fig. 3. Cell growth on the brush-type polymer surface.

of polymer chains on the surface of chemically reactive substrates, compatibility with various scaffold materials such as glass, silicon, silver, gold, and titanium, and the possibility of combining additional functional molecules [32–35]. In tissue engineering applications of brush-type polymeric structures, a suitable environment is created by planting cells on the brush structure surface (Fig. 3). By adjusting the brush structure, an environment is created in the interstitial spaces of the polymer brushes where the cells will hold and grow and multiply (Fig. 4).

2. Brush type polymers in tissue engineering

In tissue engineering, it is vital to control much behaviour of cells. Brush-type polymers play a significant role in providing this. Using brush-type polymers in tissue engineering is critical in regulating cell/stem cell behaviour and antifouling, scaffold functionalization for cell manipulations, and implant and membrane modifications. Brush-type polymers create a suitable surface for the attachment and growth of cells, especially in tissue engineering applications. For this reason, single-layer cell structures can be obtained by using brush-type polymers, as well as multilayer cell structures can be quickly produced, as shown in Fig. 5.

2.1. Brush type polymer cell layer design without scaffold in tissue engineering

In tissue engineering, polymer brush surfaces can be used as activators of cells for tissue reconstruction. Cell layers have been shown to integrate well into tissues and are promising tools for tissue reconstruction [36,37]. Cell layers prepared for tissue engineering can be used with and without scaffolding. These cellular layers obtained show good integration in the tissues. It is successfully used in severe corneal disorders, esophageal disorders, lymphocyte capture and periodontal regeneration, and impaired myocardial repair [38–44]. Cellular responses to the bioactive brush type polymer and its control over cell behaviour have been particularly studied. In this title, their use without scaffolding will be mentioned. Recent studies, especially cell culture substrates modified with a thermally responsive polymer brush, show that it controls cell adhesion, proliferation, and separation [45–48]. Atom transfer radical polymerization (ATRP), nitroxide mediated polymerization (NMP), reversible addition-fragmentation chain transfer polymerization (RAFT), anionic polymerization, click chemistry, and graft polymer modifications can be used to prepare brush-type polymers. With these methods, onto the surface of the polymer can be grafted biocompatible polymeric brush structures that cells can attach. [49]. Proteins such as gelatin and collagen are also widely used to promote cell adhesion to the brush-type polymer surface [2]. In addition, as a polymer brush structure poly(methyl methacrylate) (PMMA), poly(2-hydroxyethyl methacrylate) (PHEMA), poly(*N*-isopropyl acrylamide) (PNIPAM), poly(glycidyl methacrylate) (PGMA), poly(acrylic acid) (PAA), polycaprolactone (PCL), poly(polyethene glycol methacrylate) (PPEGMA), poly(ethylene glycol) (PEG) are widely used in tissue engineering applications (Fig. 6). Table 1 shows the polymer structures used in tissue engineering applications, their usage purposes, and the cell type they are applied to. Peptide sequences are among the most commonly used polymers to be modified with specific peptide sequences through epoxy groups that react readily with amino or carboxyl groups [50]. Under this heading, studies of brush-type polymers in tissue engineering to repair or facilitate conditions such as cell adhesion, growth, proliferation, and surface attachment are included.

The surface of brush-type polymers can create a suitable surface for the attachment and growth of cells. In addition, antifouling surfaces can be formed by attaching groups that prevent the attachment of cells or bacteria. However, viruses can be prevented from adhering to the surfaces. Fig. 7 shows the polymer structures commonly used to avoid bacteria from sticking to surfaces. As a result of bacteria colonisation on the surfaces of surgical materials and devices used in the medical field, problems arise in human health after surgeries. Therefore, antibacterial surfaces that can prevent bacterial attachment and biofilm formation have long been focused on and researched. These surfaces have become an active research area, especially with the studies in the biomedical field.

Many antibacterial strategies have been developed, and the most popular of these strategies has been the “Killing and Releasing”

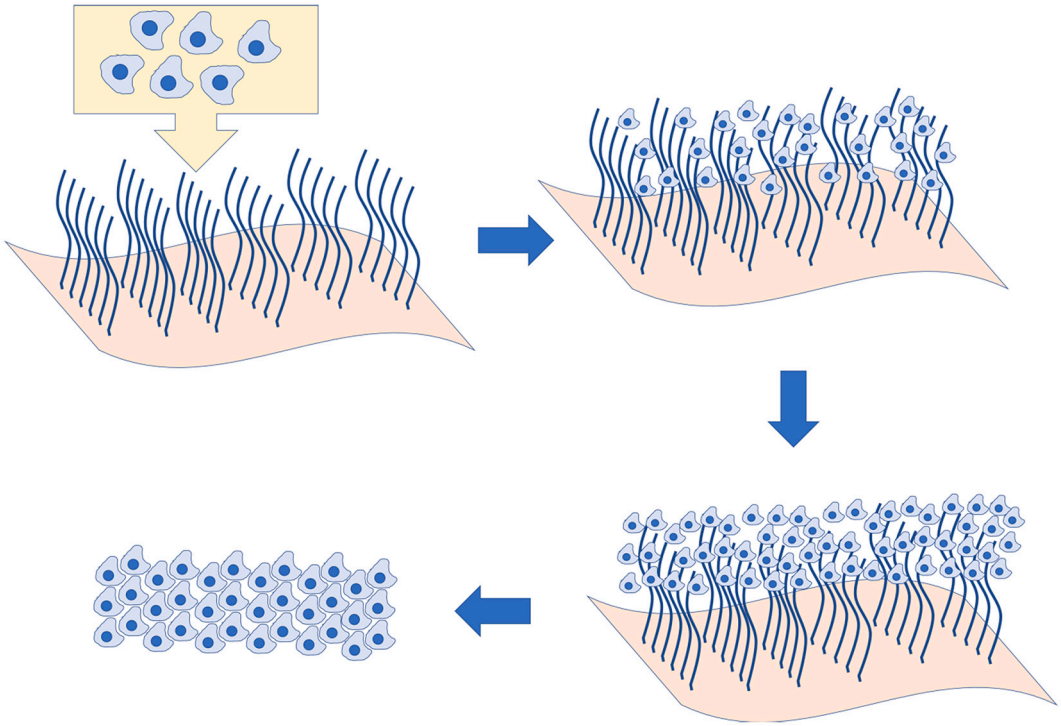

Fig. 4. Observing the formation of cell structure within the brush structure.

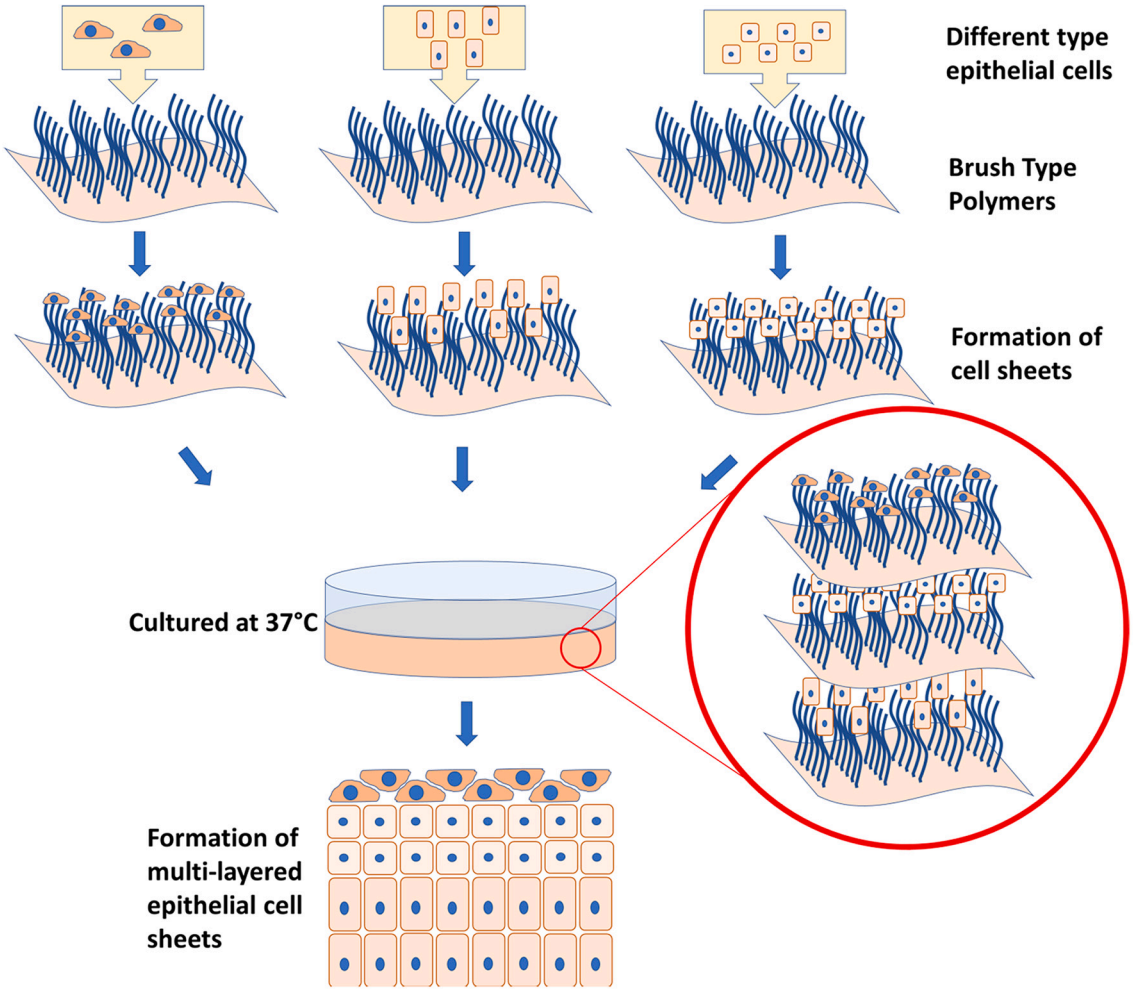

Fig. 5. Production of multilayer epithelial cell structures using brush-type polymer support materials.

technique. This strategy effectively creates smart antibacterial surfaces and is considered one of the promising techniques. These constructed surfaces can kill the bacteria adhering to them. It can then release on-demand to expose bacteria residue and other debris. Thus, the surface maintains its antibacterial properties for a long time under a suitable stimulus.

Takahashi et al. synthesized thermo-responsive poly(*N*-isopropyl acrylamide) (PIPAAm) brush surfaces with various terminal groups (maleimide, C_3H_7, COOH) by RAFT polymerization of thermosensitive polymer brush surfaces. Terminal-carboxylated PIPAAm brush surfaces allowed smooth muscle cells (SMCs) to adhere firmly to the brush surface simultaneously and rapidly separate (Fig. 8). This functionalization is very useful for the thermo-positive surface. The study can contribute to cell layer technology in tissue engineering [51].

Dworak et al. Synthesized thermosensitive poly(tri(ethylene glycol) monoethyl ether methacrylate [P(TEGMA-EE)] brushes on glass and silicon wafers with surface-initiated atom transfer radical polymerization (SI-ATRP). They worked on the thermosensitive bonding/separation of polymer brushes. Fibroblast cells adhered to P(TEGMA-EE) brush surfaces at 37 °C and spread well. The fibroblast cells were detached at 17 °C From the polymer brush layer (Fig. 9). This study shows that the heat-sensitive brush type polymer surface obtained can be successfully used as a substrate for skin tissue engineering [52].

Ghaleh et al. synthesized well-initiated and high-density poly(2-hydroxyethyl methacrylate) (PHEMA) brushes with SI-ATRP polymerization on poly (dimethylsiloxane) (PDMS) surface to impart hydrophilicity and biomolecules repellent properties. The PDMS surface coated with the PHEMA brush exhibits excellent protein and platelet resistance and repels endothelial cells. Additionally, gelatin macromolecules conjugated on linked PHEMA chains regulate the adhesion and growth of human umbilical endothelial vascular cells (HUVEC) through ligand-receptor interactions. The study is promising for cardiovascular tissue engineering [53]. Tugulu et al. obtained PHEMA and poly (polyethene glycol methacrylate) (PPEGMA) brush by SI-ATRP polymerization. PHEMA and PPEGMA6 used arginyl glycyl aspartic acid (RGD) based peptide ligands to adhere HUVEC cells to PPEGMA10 brush surfaces. HUVEC cells immobilised on peptide-functional PHEMA, PPEGMA6, PPEGMA10 polymer brush substrates were also found to maintain homeostasis when subjected to shear stresses that simulate antibacterial blood flow (Fig. 10) [54].

Raczkowska et al. obtained thermoresponsive poly(cholesteryl methacrylate) (PChMa) polymer brush. The polymer brush was used as a substrate for the granulosa cells and non-malignant bladder cancer cells (HCV29 line) cultures, as shown in Fig. 11 [55].

Takahashi et al. polymerised PIPAAm brush surfaces by the RAFT polymerization process using poly(*N*-acryloyl morpholine) (PAcMo) macro-CTAs (macro-chain transfer agents) agents were. The polymer brush surfaces aligned with normal human dermal fibroblast cells. It shows that cells and related ECM (extracellular matrix) proteins on the surface maintain their alignment (Fig. 12). The resulting surface brush polymers can create structures that mimic tissues with specific biological functions [56].

Chiang et al. incubated RBL (rat basophilic leukemia mast cells) cells on poly (acrylic acid) (PAA) brushes of different thicknesses (Fig. 13).

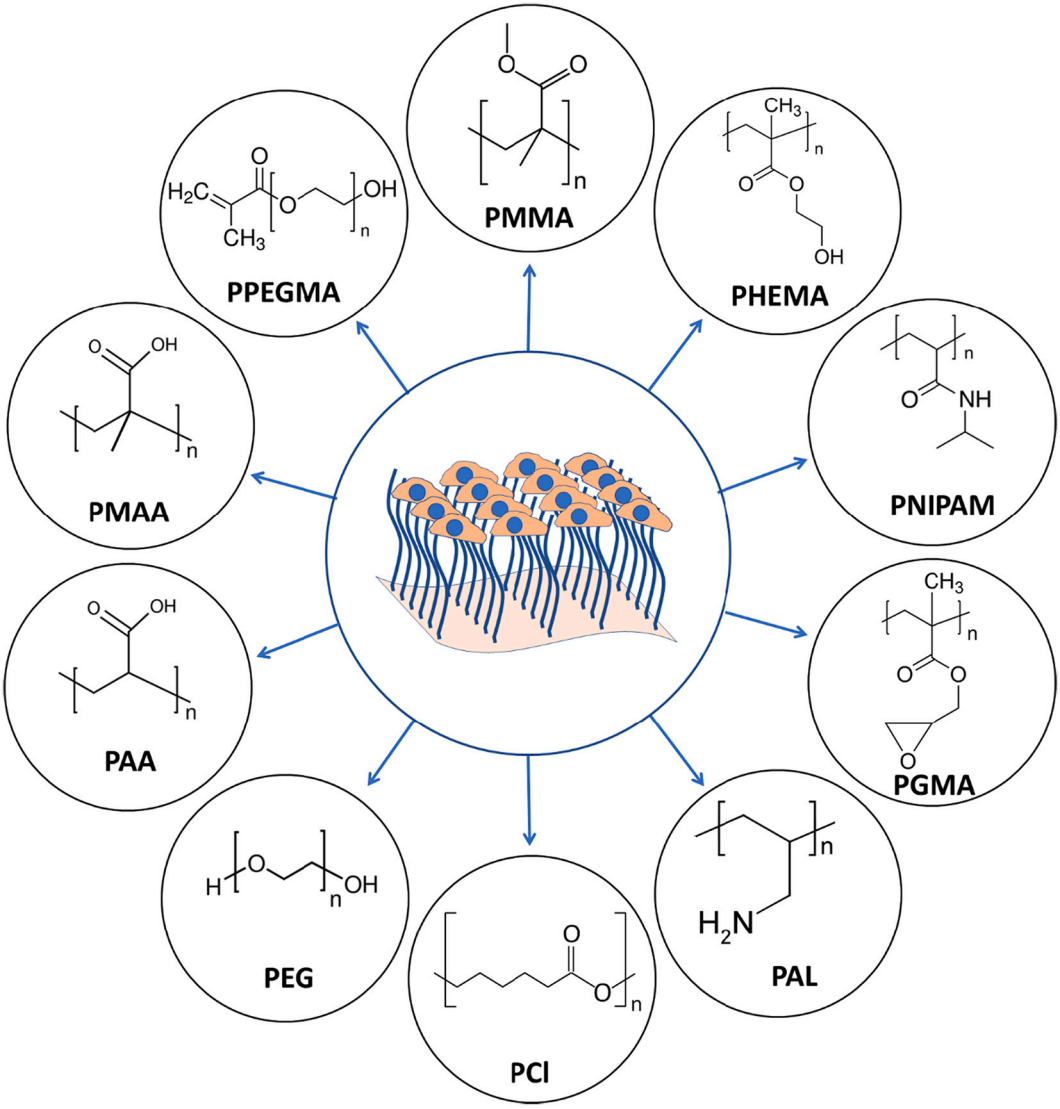

Fig. 6. Polymer brush structures commonly used in tissue engineering applications. (PMMA; poly(methyl methacrylate), PHEMA; poly(2-hydroxyethyl methacrylate), PNIPAM; poly(*N*-isopropylacrylamide), PGMA; Poly(glycidyl methacrylate), PAL; linear poly(allylamine), PCL; polycaprolactone, PEG; polyethylene glycol, PAA; poly(acrylic acid), PMAA; poly(methacrylic acid), PPEGMA; poly(poly(ethylene glycol) methacrylate).

They observed that PAA brushes of 30 or 15 nm thickness facilitated cell adhesion. PAA brushes are emphasized in tissue engineering as suitable interface substrates for cell surface receptors, especially [57].

Xu et al. prepared poly (glycidyl methacrylate) (PGMA) brushes by ATRP polymerization on polycaprolactone (PCL) film surfaces. The dense, reactive epoxide groups of the prepared P (GMA) brushes were used to immobilize collagen and Arg-Gly-Asp-Ser (RGDS) peptides in the cell (Fig. 14). Functionally criticized by PGMA brushes containing collagen and peptides, PCL film surfaces exhibited excellent adhesion to cells (3 T3 fibroblast) [58].

Wei et al. obtained hydrophilic poly(hexamethyldisiloxane) pHMDSO brushes applied on fibronectin (F.N.). They observed that more L929 fibroblast cells adhere and spread to the hydrophilic pHMDSO brush surfaces [59]. Chen et al. have developed a biomimetic nano-micro dual polymer brush system that provides adequate cell adhesion and orientation and allows intelligent separation of cells directed on external stimuli for tissue engineering applications. The nano-micro dual polymer brush system consists of gelatin modified poly (glycidyl methacrylate) (gelatin-PGMA) brushes that are spaced apart by the microstrips of the poly(*N*-isopropyl acrylamide) (PNIPAAm) brush. Gelatin-PGMA brushes are responsible for the orientation of mouse embryonic fibroblast cells (NIH-3 T3), and PNIPAAm meetings are responsible for cell adhesion [60]. Iwata et al. prepared poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) brush type polymer by ATRP polymerization. Serum protein adsorption and fibroblast cell adhesion were reduced with the PMPC brush polymer prepared in 5.5 ± 1.0 nm (3 h polymerization) thickness. The density of adherent cells on PMPC brush surfaces can be controlled by changing the size. It is thought that the study may be necessary for the formation of optimum bio-interfaces in tissue engineering and the development of antifouling properties (Fig. 15) [61].

Psarra et al. carried out the surface bio-functionalization of PAA polymer brushes with hepatocyte (HGF) and essential fibroblast growth factor (bFGF) through physisorption and chemisorption methods. The bio-functional PAA brushes obtained can regulate the differentiation of human hepatocellular carcinoma cells (HepG2) and mouse embryonic stem cells (mESC) (Fig. 16). The study shows that PAA brush polymers can be used as versatile bioactive cell culture substrates [13].

Löbbicke et al. obtained mineralised brush surfaces by mineralisation of poly(methyl methacrylic acid) (PMAA) and poly(dimethylaminoethyl methacrylate) (PDM-AEMA) brushes with calcium phosphate at different pH. The number of viable preosteoblastic cells on mineralised

Table 1
Brush type polymer cell layer design without scaffold in tissue engineering.

Structure of the brush polymer	Brush polymer morphology / Type of polymerization	Purpose of brush polymer in tissue engineering	Cell and bacteria types used	Ref.
Alanine methyl ester-containing homopolymer and the copolymer with glycine methyl ester-based vinyl monomer	Homopolymer and copolymer brush / Brushes prepared *via* surface-initiated atom transfer radical polymerization (SI-ATRP).	Production of heat-sensitive polymeric structures that allow cell adhesion and separation, polymer brushes collapse and dehydrate around 13 °C and 25 °C	NIH/3 T3 cell (at 37 °C)	[45]
Poly(*N*-isopropyl acrylamide)	Thermoresponsive polymer brush / Surface initiated reversible addition−fragmentation chain transfer (RAFT) polymerization	Optimising cell sheet harvest	Bovine carotid artery endothelial cells	[47]
Poly(*N*-isopropyl acrylamide)	Terminal-carboxylated polymer brush / surface-initiated RAFT radical polymerization	Heat sensitive surface-cell sheet engineering, low cell-adhesion strength	Smooth muscle cells	[51]
Poly[tri(ethylene glycol) monoethyl ether methacrylate]	Polymer brushes grafted onto glass and silicon wafers / The surface-initiated atom transfer radical polymerization	As a substrate in the engineering of skin tissue, in the treatment of burns and slow-healing wounds, in the transmission of cell layers	Human fibroblasts (basic skin cells)	[52]
Poly(2-hydroxyethyl methacrylate)	PHEMA-tethered PDMS substrate / Surface-initiated atom transfer radical polymerization	Developing cardiovascular tissue engineering devices	Human umbilical vein endothelial cells	[53]
Poly(2-hydroxyethyl methacrylate) or poly(poly (ethylene glycol) methacrylate)	Peptide functionalized PHEMA and PPEGMA brushes / Surface-initiated ATRP polymerization	Promote endothelialization of blood-contacting biomaterials, maintaining homeostasis against shear stresses that simulate arterial blood flow	Human umbilical vascular endothelial cells (HUVECs)	[54]
Poly(cholesteryl methacrylate)	Temperature-responsive grafted polymer brushes / Grafting onto the glass plate surface	Offers potential application as substrates for tissue engineering	Granulosa cells and a non-malignant bladder cancer cell (HCV29 line)	[55]
Poly(*N*-isopropylacrylamide)/ poly(*N*-isopropylacrylamide)-*b*-poly(*N*- acryloylmorpholine)	Functionalized thermoresponsive block copolymer / RAFT-mediated block copolymerization	The ability of engineered cell leaves to create tissue-mimicking structures with specific biological functions in cell-sheet engineering	Normal human dermal fibroblast cells (NHDFs)	[56]
Poly(acrylic acid)	Modified polymer brush conjugates / Surface-initiated ATRP polymerization	Suitable interface substrates for cell surface receptors in tissue engineering	Rat bosophilic leukemia mast cells (RBL)	[57]
Polycaprolactone-g-poly(glycidyl methacrylate)	PCL film surface with covalently bonded polymer brushes / Surface -initiated atom transfer radical polymerization	Excellent cell-adhesion property, functional and biocompatible polymeric films	3 T3 fibroblast	[58]
Poly(hexamethyldisiloxane)	Modification of organic polymers by O_2-plasma treatment / Plasma polymerization	Investigation of the effect of surface wettability on fibroblast adhesion over a wide range of wettability	Human fibroblast cells (L-929)	[59]
Gelatin-poly(glycidyl methacrylate) @ poly(*N*-isopropyl acrylamide)	Biomimic nano-micro dual polymer brush system / Surface-initiated ATRP polymerization	Cell adhesion and orientation, allows intelligent separation of cells directed on external stimuli for tissue engineering applications	Mouse embryonic fibroblast cells (NIH-3 T3)	[60]
Poly(2-methacryloyloxyethyl phosphorylcholine)	Polymer brush grafting on a silicon wafer / Atom transfer radical polymerization	Formation of optimum bio-interfaces and development of antifouling properties in tissue engineering	Fibroblast cell	[61]
Poly(acrylic)acid	Polymer brushes bio functionalized with growth factors / a “grafting to” technique	Bioactive cell culture substrates	Human hepatocellular carcinoma cells (HepG2), mouse embryonic stem cells (mESC).	[13]
Poly(methacrylic acid) and poly(dimethylaminoethyl methacrylate)	Polymer brushes on thiol-modified gold surfaces / The surface initiated free radical polymerization	The modification of surfaces in contact with hard biological tissue	Preosteoblastic cells (MC3T3-E1)	[62]
Poly oligo (ethylene glycol methyl ether methacrylate), poly(2-(methacryloyloxy)-ethyl-di methyl-(−3-sulfopropyl) ammonium hydroxide), poly(3-sulfopropylmethacrylate), poly(2-methacryloyloxy)-ethyl-trimethyl-ammonium chloride), poly(2-(methacryloyloxy) -ethyl-trimethyl-ammonium chloride)-*r*-(3-sulfopropylmethacrylate), poly(2 (methacryloyloxy) ethyl-dimethyl-(3-sulfopropyl)-ammonium hydroxide)	Bio-functionalized polymeric brush patterns / Atom transfer radical polymerization	Controlling the adsorption of extracellular matrix (ECM) proteins to well-defined micron-sized areas, controlling epidermal stem cell adhesion, spread, and shape	Cuman mesenchymal stem cells (hMSc)	[20]
Poly(ethylene glycol methacrylate)	Concentrated Polymer Brushes Presenting Different Surface Stiffness / Atom transfer radical polymerization	Biomaterial design in regenerative medicine and tissue engineering	Human mesenchymal stem cells (hMSc)	[63]
Poly(*N*-isopropylacrylamide)-*co*-*N*, *N*-dimethylaminopropylacrylamide-*co*-*N*-tert-butylacrylamide) and poly(*N*-isopropyl acrylamide-*co*-3-acrylamidopropyl trimethylammonium chloride-*co*-*N*-tert-butylacrylamide)	Thermosensitive cationic copolymer brushes / Atom transfer radical polymerization	Thermally modulated cell separation materials	Human bone marrow mesenchymal stem cells (hbmMSC)	[64]
Poly[2-(methacryloyloxy)ethyl dimethyl-(3-sulfopropyl) ammonium hydroxide]	Synthetic polymer brush coating / *Graft*-polymerization	The ability to maintain long-term cell growth and keep it in culture, elucidating the mechanism that controls hESc cell behaviour	Human embryonic stem cells (hESc)	[10]

(*continued on next page*)

Table 1 (*continued*)

Structure of the brush polymer	Brush polymer morphology / Type of polymerization	Purpose of brush polymer in tissue engineering	Cell and bacteria types used	Ref.
Poly(oligo-(ethylene glycol) methacrylate-*co*-2-hydroxyethyl methacrylate)	Peptide decorated poly(OEGMA-*co*-HEMA) brushes / Surface -initiated atom transfer radical polymerization	Long-term culturing of human-derived pluripotent stem cells (hiPSC)	Human-induced pluripotent stem cells (hiPSC)	[12]
Poly(*N*-isopropylacrylamide)	Thermoresponsive brushes / Surface-initiated atom transfer radical polymerization	Production of cell layers to be applied in biotechnology and regenerative medicine	Bovine endothelial artery cells (BAECs)	[65]
Poly(*N*-isopropylacrylamide)	Polymer brush grafted glass surfaces / Surface -initiated atom transfer radical polymerization	Protein and cell adsorption (adhesive)	Bovine carotid artery endothelial cells (BAECs)	[66]
Poly(*N*-isopropylacrylamide)	Polymer brush gradient covalently anchored on a silicon substrate / Surface-initiated atom transfer radical polymerization	Development of a method for fabricating a stable gradient surface with better quality control	Human liver cancer cell line (HepG2 cells)	[67]
Poly[2-(methacryloyloxy) ethyl dimethyl-(3-sulfopropyl) ammonium hydroxide]	Synthetic polymers brush coatings / Atom transfer radical polymerization	Increasing the ability to support hESC expansion, effective in the scalable production of hESCs for application in regenerative medicine	Mouse embryonic fibroblasts (MEFs), human embryonic stem cells (hESCs)	[68]

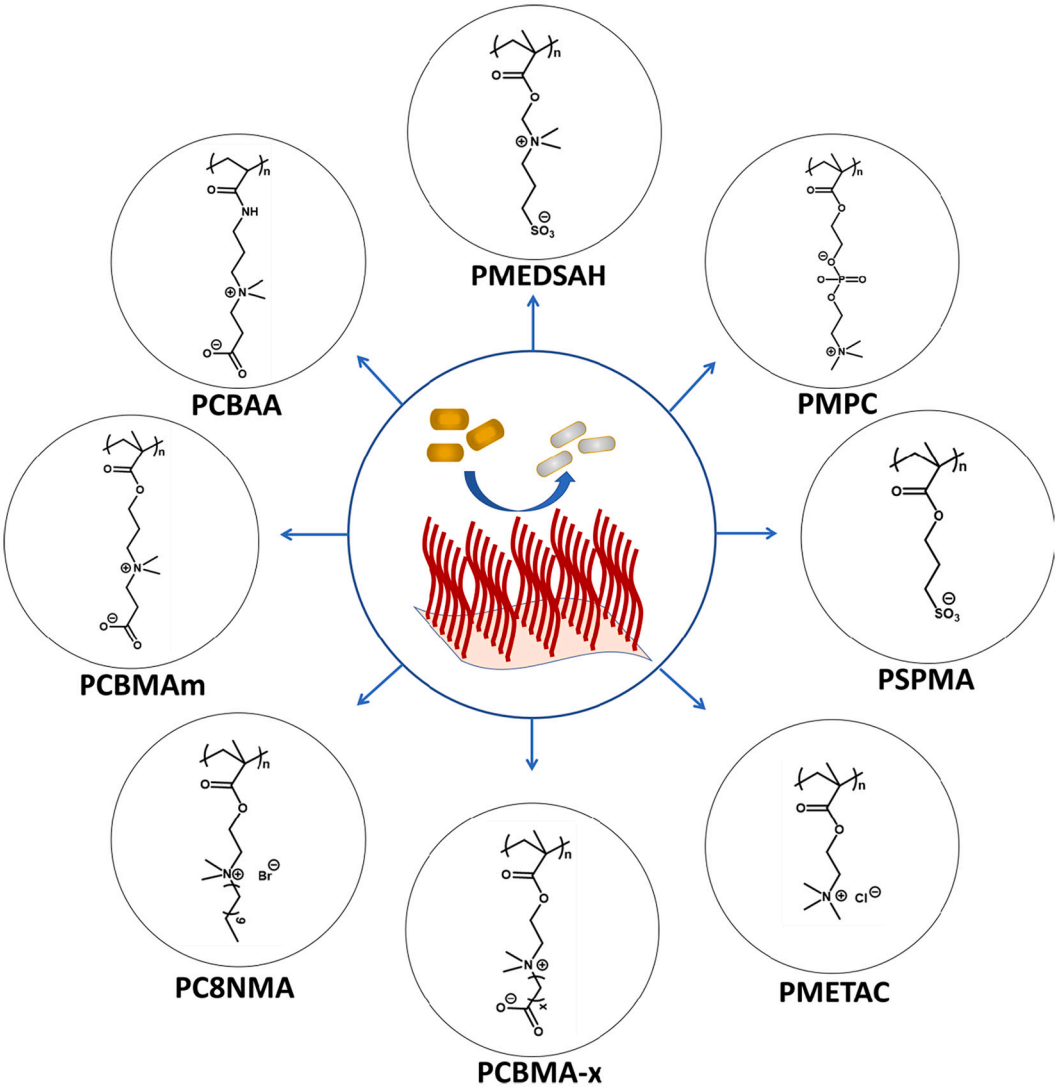

Fig. 7. Brush type polymer structures commonly used to prevent bacteria from adhering to surfaces. (PMEDSAH; poly[2-(methacryloyloxy) ethyl dimethyl-(3-sulfopropyl) ammonium hydroxide], PMPC; poly(2-methacryloyloxyethyl phosphorylcholine), PSPMA; poly(3-sulfopropyl methacrylate), PMETAC; poly((2-(methacryloyloxy)ethyl)-trimethylammonium chloride), PCBMA-x; poly(carboxybetaine methacrylate)-x, PC8NMA; poly(methacryloyloxy ethyl-dimethyloctyl ammonium bromide), PCBMAm; poly(carboxybetaine methacrylamide), PCBAA; poly(carboxybetaine acrylamide).

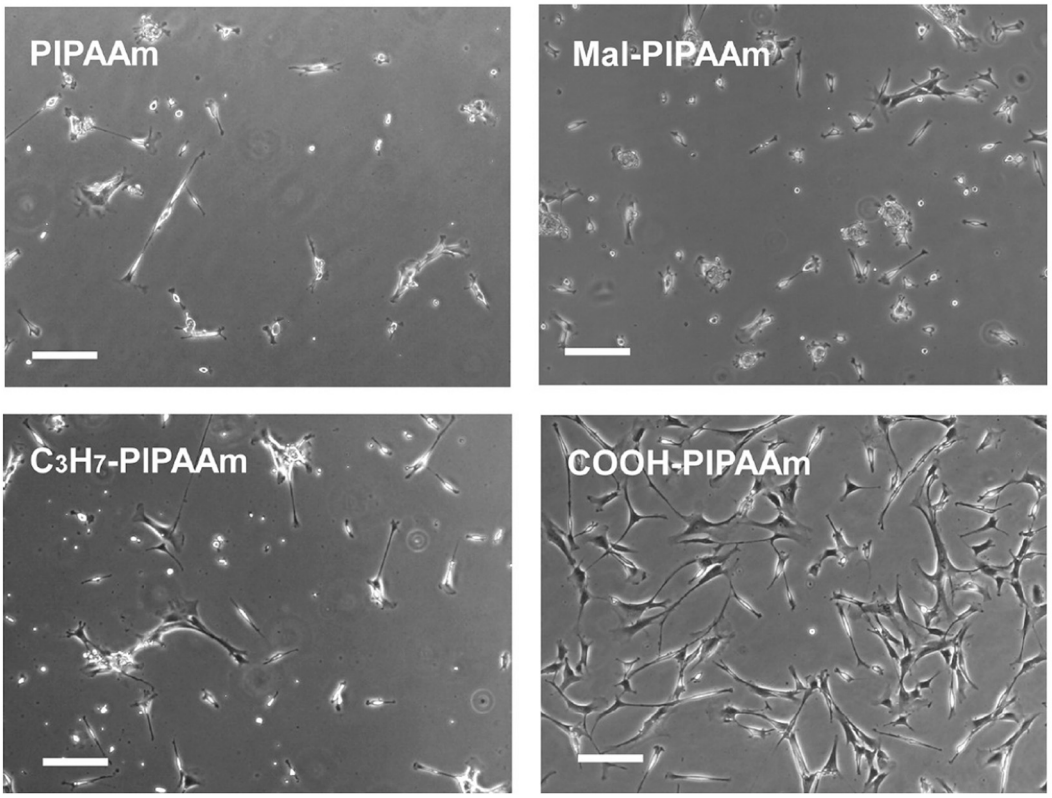

Fig. 8. Microscopic photographs of adherent smooth muscle cells on four types of PIPAAm surfaces with various terminal groups after a 24-h incubation at 37 °C (Scale bar: 100 μm) [51].
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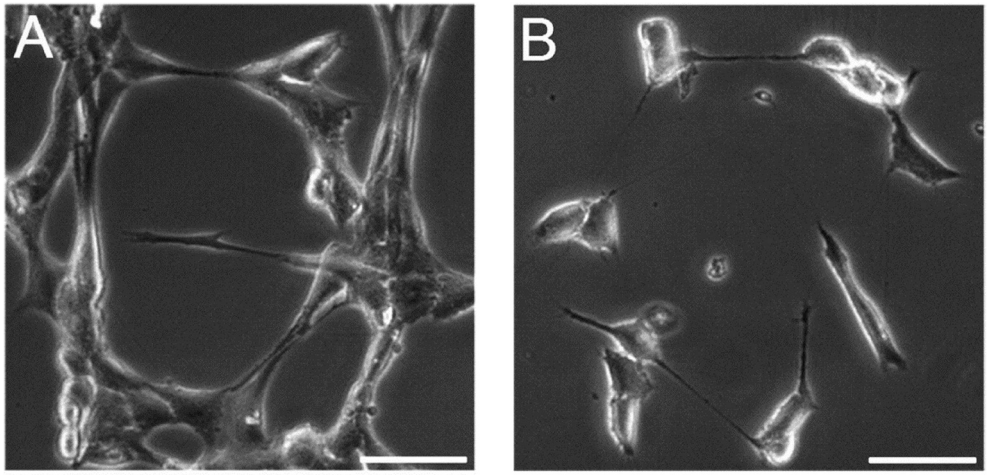

Fig. 9. Images of single fibroblasts on the Si ~ P(TEGMA-EE)-21 h surface after (A) 24 h of incubation at 37 °C and (B) 20 min after cooling the sample to 17.5 °C (Scale bar: 100 μm) [52].
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brush surfaces was relatively high compared to non-mineralised surfaces. Mineralisation significantly increases cell adhesion and growth (Fig. 17). The polymerization/mineralisation initiated at the working surface is a promising approach for modifying surfaces in contact with hard biological tissue [62].

The surface morphology and chemistry of brush polymers strongly influence the adhesion and behaviour of human mesenchymal stem cells. Tan et al. present micro-patterned poly oligo (ethylene glycol methyl ether methacrylate) (POEGMA), poly(2-(methacryloyloxy)-ethyl-di methyl-(−3-sulfopropyl) ammonium hydroxide) (PMEDSAH), poly(3-sulfopropylmethacrylate) (PSPMA), poly(2-methacryloyloxy)-ethyl-trimethyl-ammonium chloride) (PMETAC), poly(2-(methacryloyloxy)-ethyl-trimethyl-ammonium chloride)-*r*-(3-sulfopropylmethacrylate) (COPO) polymer brushes to control the adsorption of extracellular matrix (ECM) proteins to well-defined micron-sized areas and control epidermal stem cell adhesion, spreading, and shape [20].

Nam et al. obtained poly(ethylene glycol methacrylate) PPEGMA brushes coated with collagen. They observed that human mesenchymal stem cells (hMSc) react differently between highly concentrated PPEGMA and moderately concentrated PPEGMA brushes. The hMSc

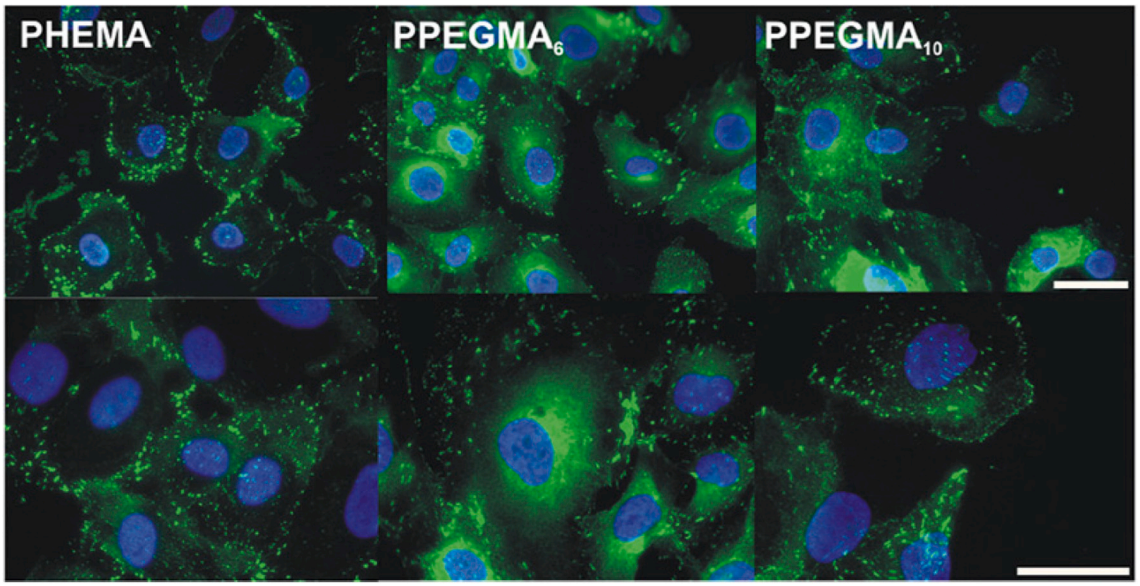

Fig. 10. Overlay of fluorescence micrographs of HUVECs 4 h post-seeding adhering to GGGRGDS functionalized 20 nm thick PHEMA, PPEGMA6 and PPEGMA10 brushes stained for nuclei (DAPI) and vinculin (Scale bar: 25 mm) [54].
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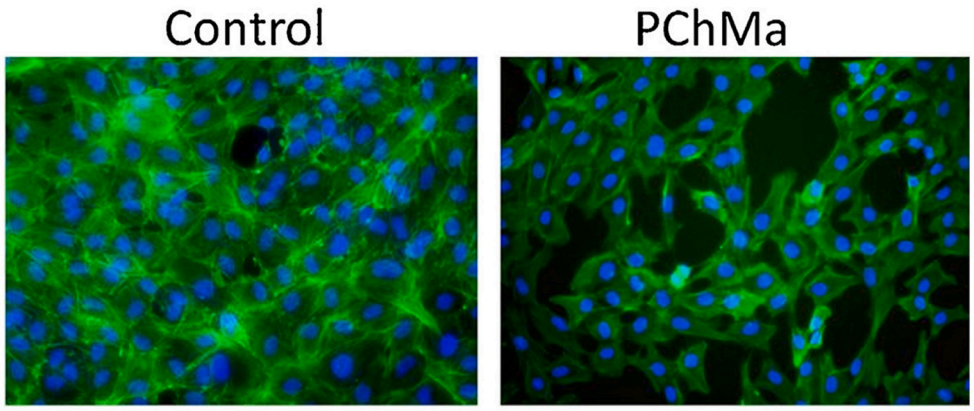

Fig. 11. Fluorescent images of HCV29 bladder cancer cells after 72 h culture on glass and PChMA (200× magnitude) [55].
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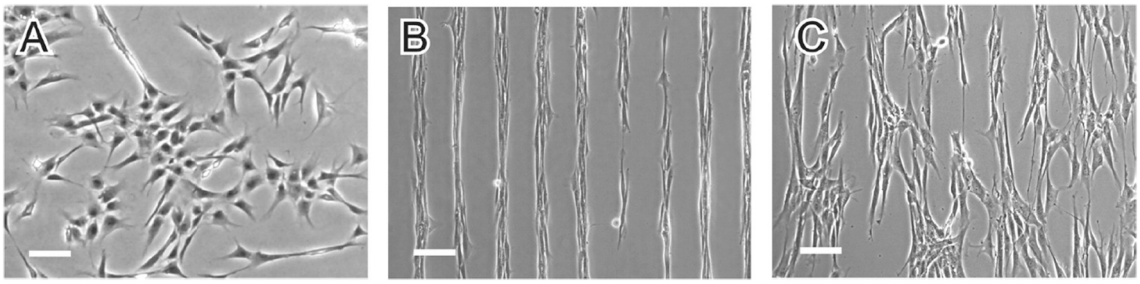

Fig. 12. Microscopic photographs of adherent fibroblasts on (A) nonpatterned PIPAAm brush surfaces and (B,C) PIPAAm/PIPAAm-b-PAcMo patterned brush surfaces (stripe pattern width: 50 μm). The photographs were taken at (A, B) 24 and (C) 48 h after the cell seeding. (Scale bar: 100 μm) [56].
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cells did not adhere to the high-density brush polymer. The work will progress in biomaterial design that can be applied to tissue engineering [63]. Thermosensitive cationic poly(*N*-isopropyl acrylamide-*co*-*N*,*N*-dimethylamino propyl acrylamide-*co*-*N*-tert-butylacrylamide and poly (*N*-isopropylacrylamide-*co*-3-acrylamidopropyl trimethylammonium chloride-*co*-*tert*-*butylacrylamide*) copolymer brushes were prepared by SI-ATRP polymerization on glass surfaces by Nagase et al. The prepared cationic copolymer brushes affected the adhesion / detachment behaviour of human bone marrow mesenchymal stem cells (hbmMSc) due to varying temperatures. Only hbm MSC cells adhered to the brush at 37 °C

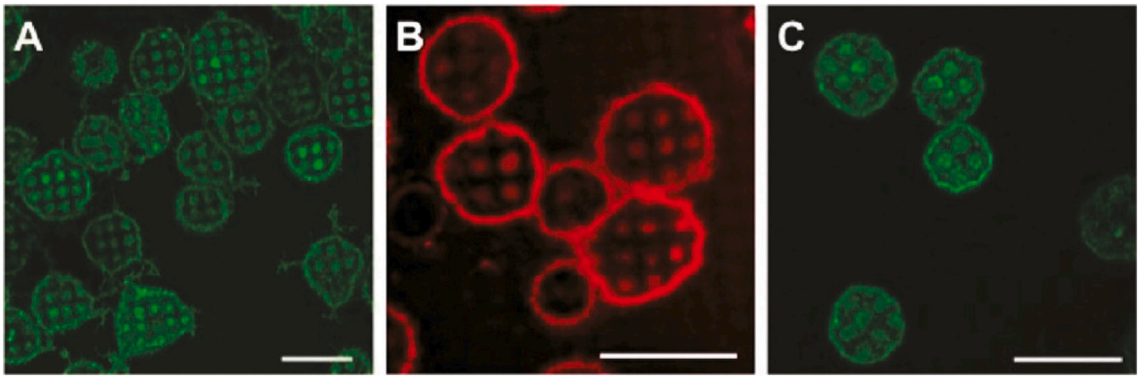

Fig. 13. Cell membrane accumulates over patterned PAA brushes with small feature sizes. Representative fluorescence micrographs of cells incubated with substrates patterned with two μm squares of PAA brushes (30 nm thick). Cells were labelled with A488IgE (A), TRDPPE (B), or A488CTxB (C). (The scale bar is 20 μm) [57]. Reprinted with the permission of Ref [57] Copyright 2011 American Chemical Society.

and hbm MSC cells were separated from the brush surface when the temperature dropped to 20 °C. These results are thought to be useful with the prepared cationic copolymer brush in the purification of hbm MSC from bone marrow and separation of hbm MSC and other somatic cells (Fig. 18) [64].

The work done by Villa-Diaz et al. showed that human embryonic stem cells (hESc) on poly(2-(methacryloyloxy)ethyl dimethyl-(3-sulfopropyl)ammonium hydroxide) (PMEDSAH) polymer brush could sustain long-term cell growth and keep them in culture. With this aspect, the study is essential in elucidating the mechanism that controls hESc cell behaviour [10].

Deng et al. used SI-ATRP polymerization to prepare vitronectin (V.N.) peptide-linked poly(oligo-(ethylene glycol) methacrylate-*co*-2-hydroxyethyl methacrylate) poly(OEGMA-*co*-HEMA) brushes. The use of V.N. bonded poly(OEGMA-*co*-HEMA) brushes in tissue engineering is because they are an ideal platform for long-term culturing of human-derived pluripotent stem cells (hiPSC) [12]. We can see the microscope image of the peptide-decorated surface in Fig. 19.

Mizutani et al. prepared thermo-responsive poly(*N*-isopropylacrylamide) PIPAAm brush surfaces in different layer thicknesses on polystyrene substrates with SI-ATRP polymerization. Adhesion/separation controls of bovine endothelial artery cells (BAECs) were performed on the prepared PIPAAm brush surfaces of different layer thicknesses. Negligible protein adsorption and negligible cell adhesion were observed on high thickness PIPAAm brush surfaces. In addition, endothelial cell layers were prepared using PIPAAm brush surfaces. We see the images of the endothelial cells on the brush surface under the phase-contrast microscope in Fig. 20. The study is also essential in tissue engineering in terms of allowing the selection of the surface during the preparation of cell layers [65].

Nagase et al. prepared PIPAAm brush surfaces with different densities and chain lengths employing SI-ATRP. Unlike the study by Mizutani et al., they observed that PIPAAm brush lengths affect cell adhesion. Adhesion of BAECs cells to the brush surface decreases inversely with increasing PIPAAm brush length. The importance of the changing properties of brush-type polymers on cellular adhesion/dissociation is emphasized once again [66].

In their study, Li et al. synthesized thermosensitive PNIPAAm brushes of different sizes using the SI-ATRP technique. The synthesized brushes cell adhesion/detachment properties were examined in HepG2 cells. HepG2 cells exhibited good adhesion at 37 °C on bushes below 20 nm. It was observed that HepG2 cells were easily separated from the surface in brushes with a thickness of more than 45 nm (Fig. 21). The study offers a wide range (20-45 nm) of thermosensitive PNIPAAm brushes to manipulate cell attachment/separations necessary in tissue engineering [67].

Qian et al. determined the effects of PMEDSAH brush structures on self-renewal of human embryonic stem cells (hESCs) using the ATRP technique. We see that PMEDSAH brush structures affect the expansion of hESc after grafting on the gel in Fig. 22. An ATRP PMEDSAH coating of 105 nm thickness showed a significant increase in the growth rate of hESCs. 20.000 hESC cells cultured on PMEDSAH substrate increased in 5 weeks to 4.7×10^9 cells. In addition, hESCs grown on PMEDSAH brush surfaces preserved pluripotency and displayed a normal karyotype after prolonged culture. PMEDSAH can be used to obtain the cell populations required for many regenerative applications of brush-type polymers in tissue engineering [68].

2.2. *Brush type polymer scaffold cell layer design in tissue engineering*

Scaffolds are widely used as tissue engineering scaffolds [69]. A scaffold is a 3D-dimensional structure that temporarily supports isolated cells to become new tissue before being transplanted back into the host tissue [70,71]. The scaffold pore structure is essential in ensuring adequate nutrient transport to cells and removing waste cells. Studies show that 3D porous scaffolds improve cell growth and differentiation by improving cell attachment and proliferation (Fig. 23). In Table 2, scaffold structured brush-type polymer applications are given in general. In these applications, scaffolds should be biocompatible, contribute to tissue regeneration, and support cell attachment and proliferation to the surface [72–77]. Studies suggest that microstructure in scaffolds improves tissue organization and causes tissue function to increase [78–81].

In tissue engineering, material chemistry, porosity, pore size, mechanical properties, and cell density significantly affect the cellular response in a cell-scaffold structure [82]. Today, tissue engineering produces 3D scaffolds from natural and synthetic polymers that provide various environments for cell adhesion, proliferation, and specific cell differentiation [83–85]. Brush-type polymers have been widely used in scaffolds for tissue engineering [33]. For use in tissue engineering, research is currently being conducted to create and control microenvironments on the scaffold surface using brush-type Polymer to develop cell-compatible properties and modulate stem cell differentiation on the adapted surface [86]. Gunnewiek et al., in their studies, fabricated 3D microporous PCL scaffolds using a rapid prototyping technique. Then, after polymerization with SI-ATRP from PCL substrates, they produced PCL-POEGMA brush-aided scaffold with POEGMA brush-coated 3D protein (ECM, BSA, F.N.) gradients with an average brush thickness of 15 nm. They used it as an application platform for the immobilisation of hMSc stem cells. Cell immobilisation and viability were well observed on the platform. Gunnewiek et al. confirmed that the prepared 3D PCL-POEGMA brush-assisted scaffolds represent a highly efficient strategy for controlling spatial cell adhesion [87].

Duque-Sanchez et al. performed the functionalisation of the brush

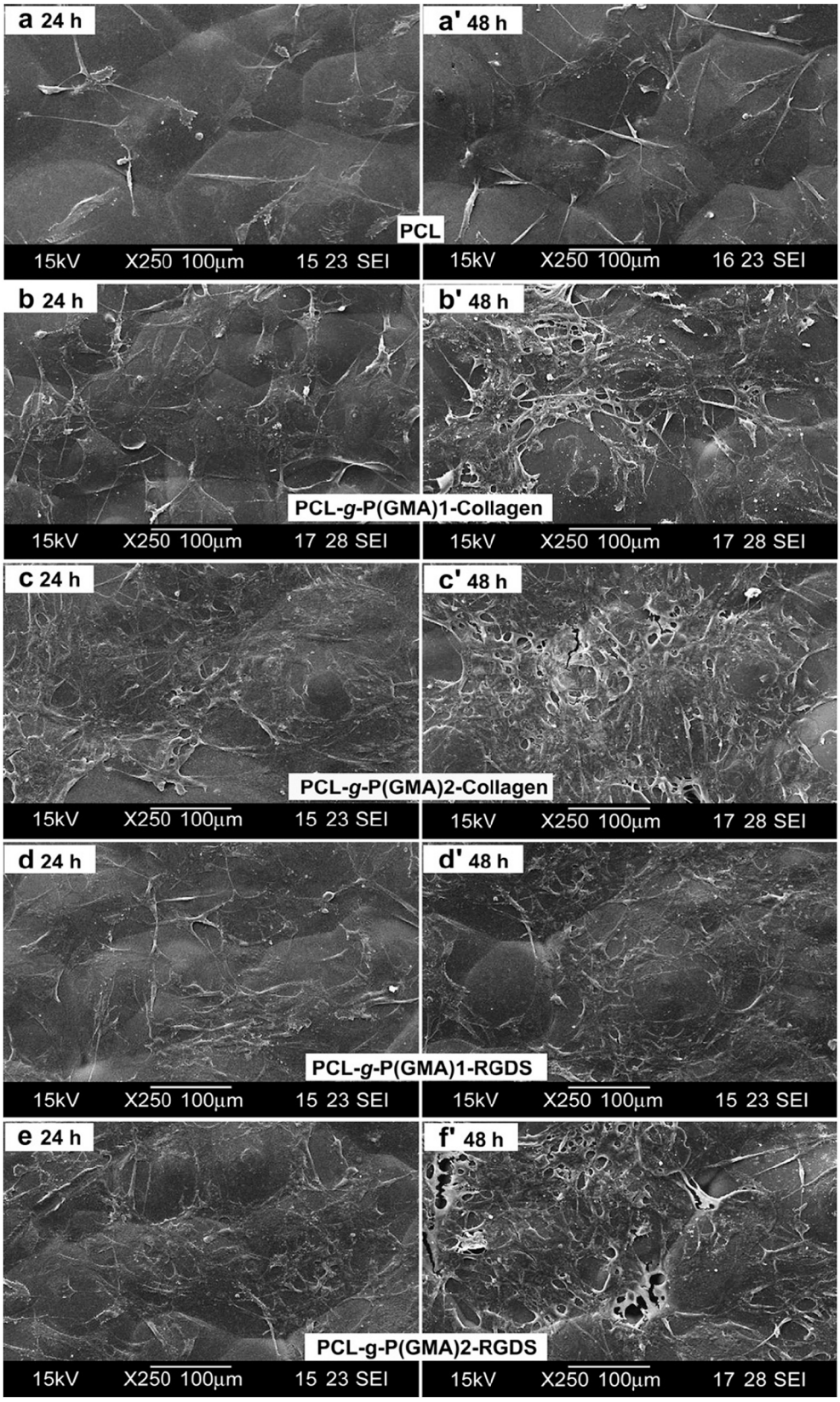

Fig. 14. SEM images of 3 T3 fibroblasts cultured for 24 and 48 h on the PCL, PCL-*g*-P(GMA)1-Collagen (from 1 h of ATRP), PCL-*g*-P(GMA)2-Collagen (from 4 h of ATRP), PCL-g-P(GMA)1-RGDS, and PCL-*g*-P(GMA)2-RGDS surfaces [58].
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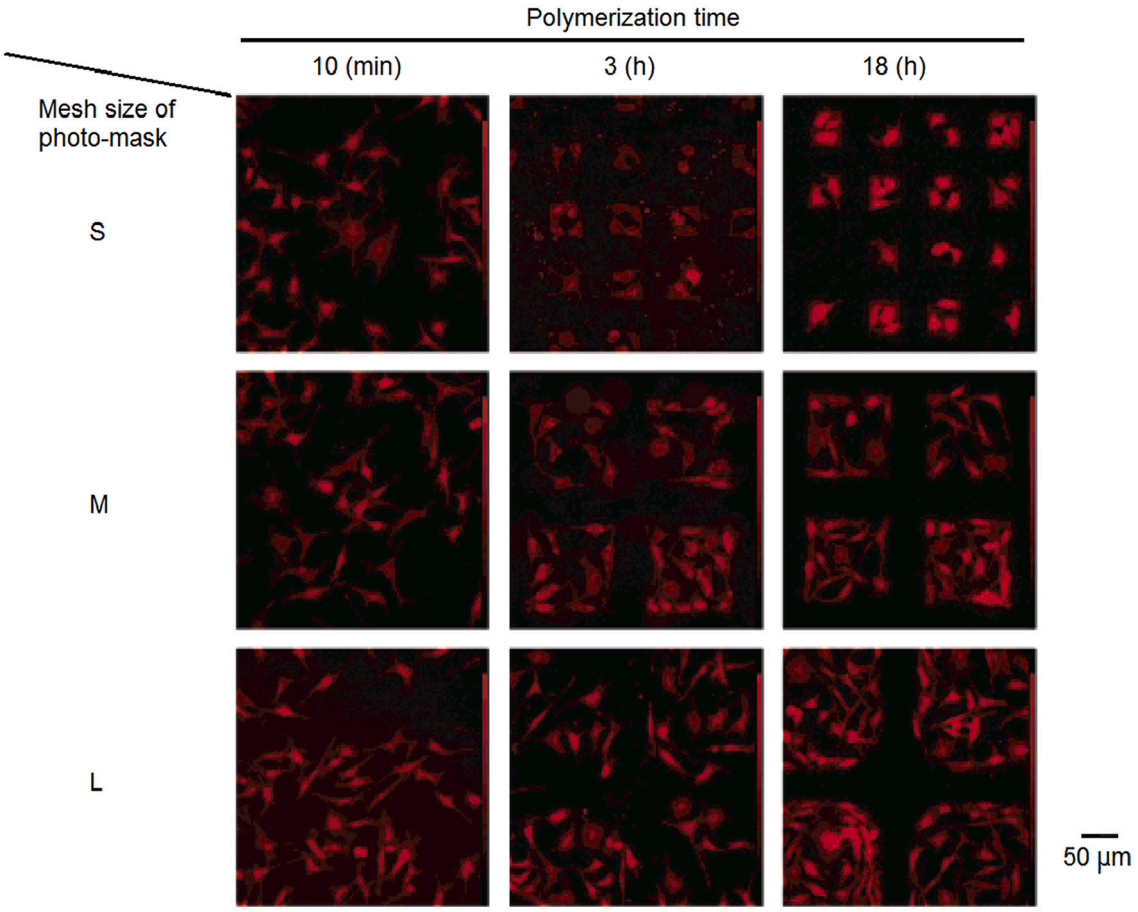

Fig. 15. Fluorescence micrographs of fibroblast adhesion on patterned PMPC brush surface after incubation for 20 h. [Fibroblast]) 5.0 × 104 cells/mL [61]. Reprinted with the permission of Ref [61] Copyright 2004 American Chemical Society.

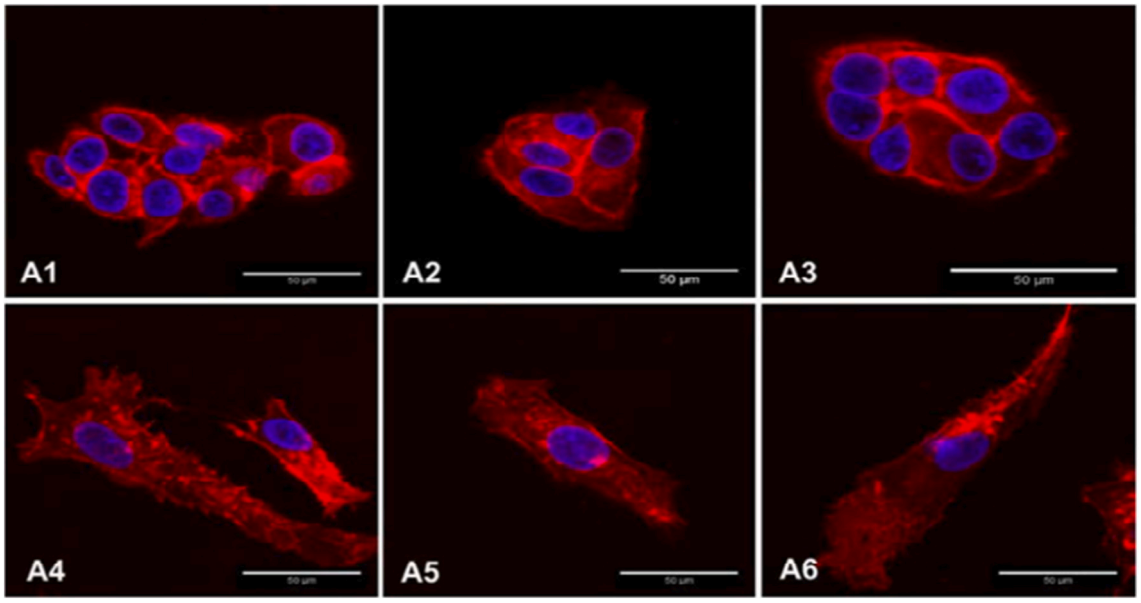

Fig. 16. HepG2 immunostaining shows the scattering effect of HGF on HepG2 cells. Nuclei are stained with DAPI (blue), and cytoskeletal F-actin filaments are rhodamine-phalloidin labelled (red). A1 - TCPS plate, A2-TCPS with soluble five ng/ml HGF, A3 - PAA brushes without HGF, A4- PAA brushes with soluble HGF, A5-PAA brushes with physisorbed HGF, A6-PAA brushes with chemisorbed HGF (scale bars 50 μm) [13]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
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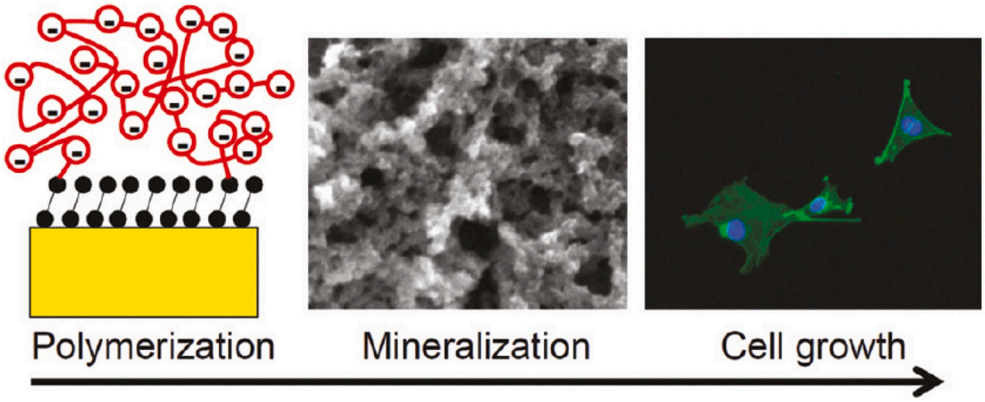

Fig. 17. Schematic representation of PMAA and PDM-AEMA brushes affects mineralisation and cell adhesion/growth [62].
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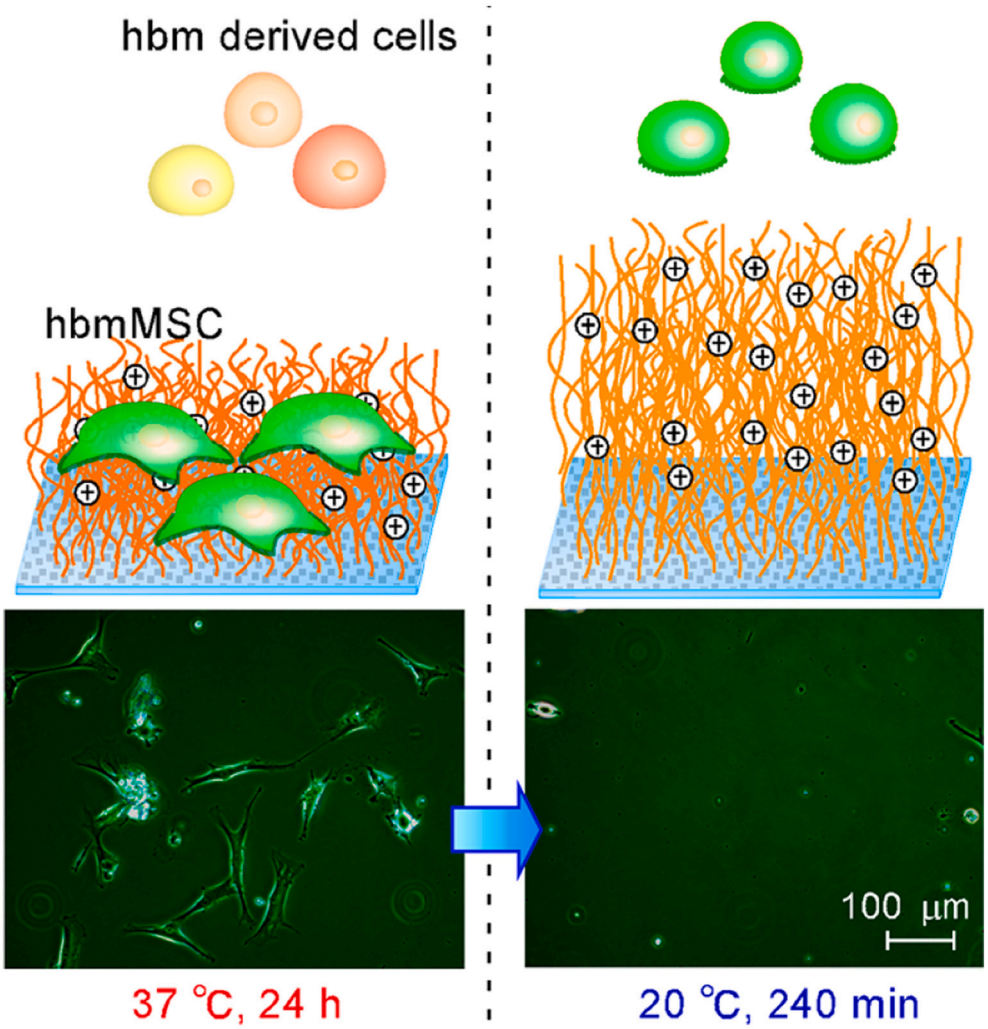

Fig. 18. Cell morphologies at 37 and 20 °C, observed after 24 and 4 h incubations, respectively [64].
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surface of poly (lactide-*co*-glycolide) (PLGA): bromine terminated poly (L-lactide)(PLA-Br) electrospun with a bioactive c (RGDfk) and non-bioactive c (RADfk) peptide conjugation. A high rate of hMSc binding has been observed by increasing the peptide concentration immobilised to the brushes [88]. In the studies of Liao et al., γ-benzyl-L-glutamate (PBLG) brushes were modified to strengthen compatibility between Hydroxyapatite (H.A.) and poly (L-lactic acid) (PLLA) composites. For bone tissue healing after modification, poly (γ-benzyl-L-glutamate) modified hydroxyapatite / (poly (L-lactic acid) (PBLG-*g*-HA / PLLA) porous structure scaffolds were prepared by thermally stimulated phase separation method. They obtained new porous scaffolds from prepared PBLG-*g*-HA / PLLA. *In vivo* bone repair experiments observed that PBLG-

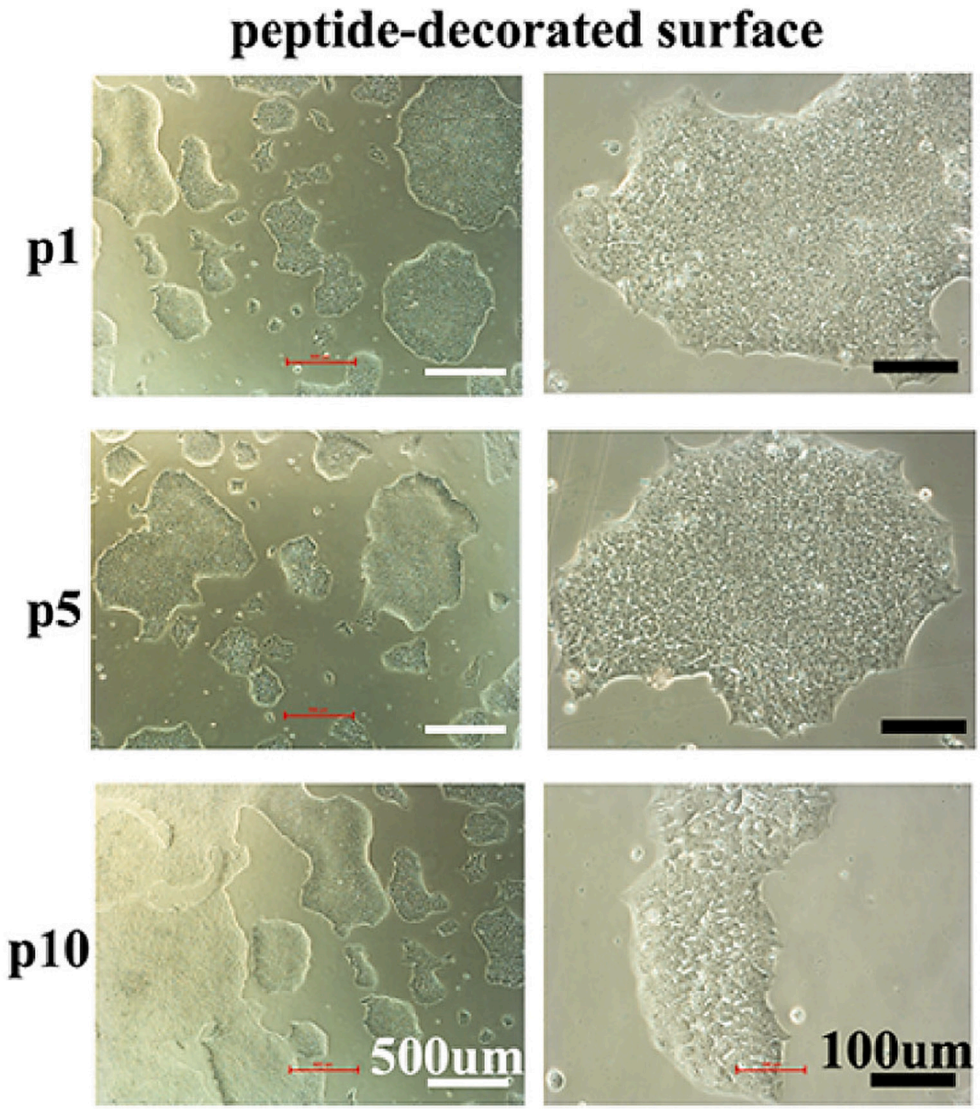

Fig. 19. The microscopic images of the morphology of hiPSC colonies (4× and 20×) were continuously cultured at passage 1, passage five and passage 10: (a) peptide-decorated substrate [12].
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g-HA / PLLA scaffolds induced higher levels of new bone formation and had little effect on osteoclastogenesis. The study made positive contributions to bone tissue repair [89].

Terzaki et al. synthesized poly(2-dimethylamino ethyl) methacrylate) (PDMAEMA) brushes on glass substrates functionalised with an initiator for bone tissue regeneration. Synthesized PDMAEMA based 3D scaffolds were prepared from synthesized PDMAEMA brushes. It was observed that mouse calvaria pre-osteoblastic cells (MC3T3-E1) adhered well to the prepared scaffolds and showed increased proliferation. It is thought that the use potential of the newly designed PDMAEMA based 3D scaffold in tissue engineering will be high [90].

2.3. Implant and membrane designs with brush type polymer in tissue engineering

Brush-type polymers have been widely studied in tissue engineering and cell or tissue augmentation applications. In addition to these applications, brush-type polymer structures have been used to coat implant surfaces, increase the tissue compatibility of implants, or provide antibacterial properties to implant structures. It has also been tried in the preparation of some membrane structures. Brush-type polymer structures used in the implant and membrane designs in tissue engineering and their usage purposes are given in Table 3.

Modifications and membrane designs made to improve implant performance with brush-type Polymer are very important in tissue engineering. Polymer brushes have become a widely used tool to change surface properties [91]. There are many implant and membrane surface studies whose functionality and bioactivity have been modified with brush-type polymers. A new functional, bioactive pluronic F-127: PF127 Polymer conjugated with antimicrobial peptides (AMP) and arginine-glycine-aspartate peptides (RGD) with antibacterial properties, effectively enabling cell (human fibroblast cells) adhesion / spreading and promoting tissue integration brush implant coating surface (Fig. 24) has been improved by Muszanska et al. [15].

Alas et al., in their work, obtained oligo(ethylene glycol)methacrylate (OEGMA) brush type polymer by SI-ATRP polymerization. Poly (OEGMA) brush consists of a poly (methacrylate) backbone with other poly (ethylene glycol) (PEG) side chains. This substrate provides the hydrophilic property that resists brush protein adsorption and cellular binding. Poly(OEGMA) brushes significantly reduce protein adsorption and cell adhesion. Clearly, we see that the poly(OEGMA) brush structure prevents cell adhesion in Fig. 25. For cell adhesion control, brush

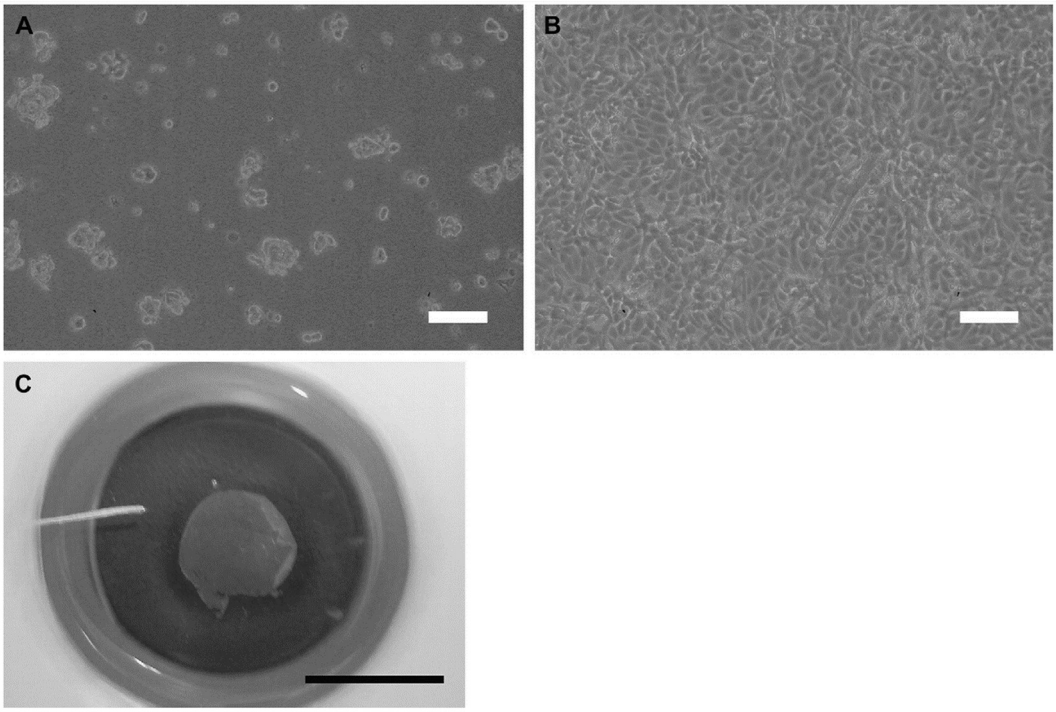

Fig. 20. Morphologies of (A) adhered ECs on brush-300-0.5 after 3 days incubation at 37 °C observed under a phase-contrast microscope, (B) confluent cultures of ECs on brush-200-0.5 after 3 days incubation at 37 °C observed under a phase-contrast microscope, and (C) detached EC sheet from brush-200-0.5 after 2 h incubation at 20 °C. Scale bars: (A, B) 100 mm and (C) 1 cm [65].
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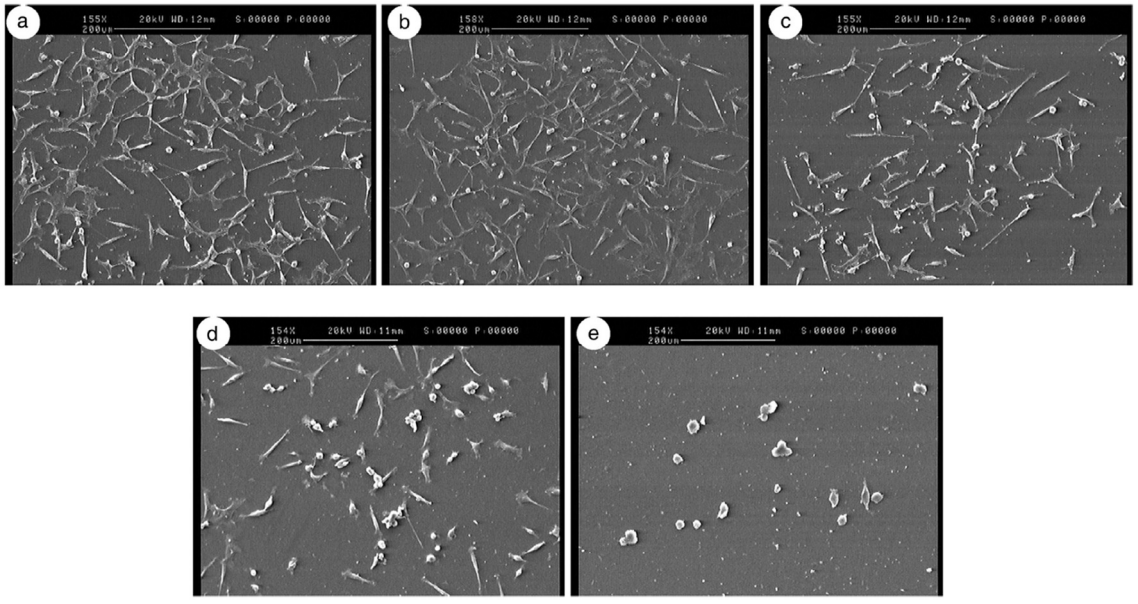

Fig. 21. SEM images of HepG2 at 0, 6, 12, 18, and 24 mm from (a) to (e), respectively. The cells were cultured at 37 °C for 8 h [67].
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surfaces allow bioactive peptide ligands such as RGD. The study emphasises that stainless steel implants may be an appropriate application in promoting bone growth and regeneration in bone tissue engineering, osseointegration improvement, and surgical bone repair [92].

Ren et al. primarily deposited a Ti surface on a poly (oligo-ethylene glycol methacrylate-*r*-2-hydroxyethyl methacrylate [p(OEGMA-*r*-HEMA)] brush by SI-ATRP polymerization in their study. In addition, fibronectin (F.N.) and recombinant human bone morphogenetic protein-2 (rhBMP-2), p(OEGMA-*r*-HEMA) were immobilised on the brush (Fig. 26). It has been shown that the resulting new brush surface can induce mouse preosteoblast cell (MC3T3) adhesion. This study can be promising in implant modifications and functionalization and provide bio-functional properties such as antifouling and osseointegration to titanium surfaces with the help of modified p (OEGMA-*r*-HEMA) brushes [93].

Liu et al. performed the covalent grafting of zwitterionic poly

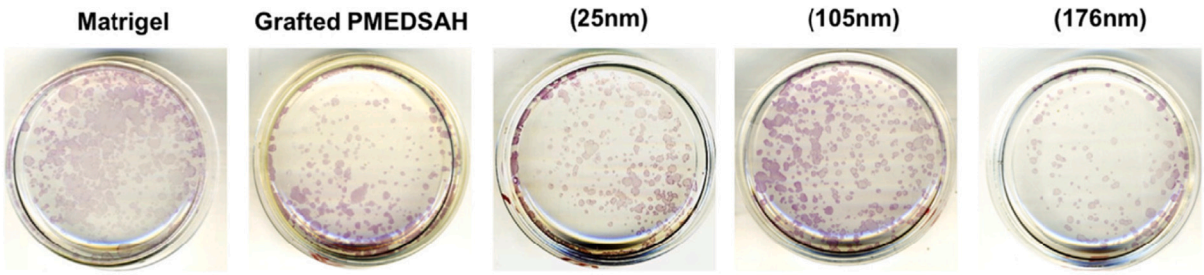

Fig. 22. Gel architecture influences the undifferentiated colony formation and expansion of hESCs. Undifferentiated colonies were identified by alkaline phosphatase staining after 7 days of culture on different substrates. [68].
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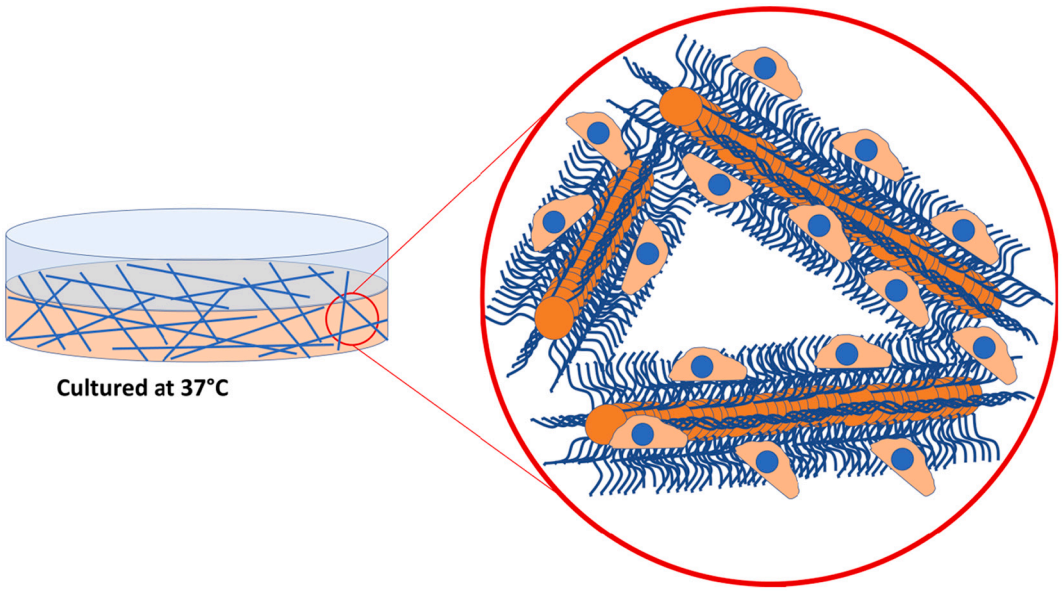

Fig. 23. Cell adhesion on polymer brushed scaffolds in tissue engineering applications.

Table 2
Brush type polymer scaffold cell layer design in tissue engineering.

Structure of the brush polymer	Brush polymer morphology / type of polymerization	Purpose of brush polymer in tissue engineering	Cell and bacteria types used	Ref.
Poly(*N*- isopropylacrylamide)	Based on the mesoporous hydroxyapatite capped with poly(*N*-isopropylacrylamide) / Surface-initiated atom transfer radical polymerization	Used as a bone substitute with sustained release of osteogenic drugs	Bone marrow mesenchymal stem cell (BMSC)	[82]
Poly(*N*-isopropylacrylamide)-Poly(*N*-acryloyl morpholine)	Thermoresponsive polymer / "grafting-to" method	Production of well-organized textures that mimic the structure and function of natural tissues	Human skeletal muscle myoblasts, human umbilical vein endothelial cells	[83]
Poly(oligo (ethylene glycol) methacrylate)	Hydroxyl functions of the grafted polymer / Surface-initiated atom transfer radical polymerization	Developing a new manufacturing strategy that includes a practical and affordable 3D ECM structure that shows versatile variations of (bio) chemical media	Human mesenchymal stem cells hMSCs	[87]
Poly(lactide-*co*-glycolide) and bromine terminated poly(L-lactide)	Copolymer brush / Surface-initiated atom transfer radical polymerization and Cu(0)-mediated radical polymerization	As scaffolds for regeneration of tissues,3D architectures used to study cell and bacterial adhesion and migration in 3D environments	Human mesenchymal stem cells (hMSCs)	[88]
Poly(γ-benzyl-L-glutamate) Hydroxyapatite / poly(L-lactic acid)	Polymer composite scaffolds / Ring opening polymerization	Developing a porous type of scaffold for bone tissue healing, bone tissue engineering or orthopedic surgery	Tartrate-resistant acid phosphatase (TRAP) TRAP-positive cell	[89]
Poly(2-dimethylamino ethyl) methacrylate)	Hybrid and organic materils / Surface initiated atom transfer radical polymerization	Production of high precision scaffolds with complex geometries and architectures for tissue engineering, bone tissue regeneration, excellent mechanical properties	Mouse calvaria pre-osteoblastic cells (MC3T3-E1)	[90]

(sulfobetaine methacrylate) (pSBMA) brush with SI-ATRP technique on Ti6A14V substrates to promote surface mineralisation of hydroxyapatite. The brush surface coating obtained shows a stable superhydrophilic property and low contamination. *In vitro* studies have been performed in rat bone marrow-derived stromal cells (rMSCs). At the end of the study, the surface mineralisation increased significantly on the surfaces

Table 3
Brush type polymer structures used in the implant and membrane designs in tissue engineering.

Structure of the brush polymer	Brush polymer morphology / Type of polymerization	Purpose of brush polymer in tissue engineering	Cell, bacteria *etc.* types used	Ref.
Bioactive pluronic F-127: PF127- antimicrobial peptides (PF127-AMP pluronic F-127: PF127-arginine−glycine−aspartate (RGD) peptides	Polymer−peptide conjugates / Antiadhesive polymer brushes, block copolymer,	Antiadhesive and bactericidal properties, tissue integrating properties, polymer brushes that repel contaminating bacteria, kill adherents and promote tissue integration	Human fibroblast cells (L-929) and three bacterial strains, *S. aureus*, *S. epidermidis*, *P. aeruginosa*	[15]
Poly(oligo (ethylene glycol) methacrylate	Non-fouling polymer brushes-adhesive peptide conjugates / Atom transfer radical polymerization	Promoting bone growth and regeneration in bone tissue engineering, osseointegration improvement, surgical bone repair	Human mesenchymal stem cells (hMSCs)	[92]
Poly(oligo-ethylene glycol methacrylate-r-2-hydroxyethyl methacrylate	Low-density ethylene glycol-terminated polymer brushes / Surface-initiated atom-transfer radical polymerization	Production of titanium-based biomedical devices for antifouling properties and immobilisation of osteogenetic and bioadhesive ligands	Mouse preosteoblast cell (MC3T3)	[93]
Poly(sulfobetaine methacrylate)	Grafting of zwitterionic brushes from the Ti6Al4V substrate / Atom transfer radical polymerization	Improving metallic implant performance production of multifunctional surface coatings	Rat bone marrow-derived stromal cells (rMSCs)	[94]
Poly(*N*,*N*-dimethyl acrylamide) / poly(*N*-(3-aminopropyl) methacrylamide)	Copolymer brushes-peptide conjugation / Surface initiated atom transfer radical polymerization	Implants resistant to tissue infection, excellent broad spectrum antimicrobial activity	Human osteosarcoma (MG-63), *S. aureus*, *P. aeruginosa*	[95]
Poly(2-methacryloyloxyethyl phosphorylcholine)	Zwitterionic polymer brushes / Surface-initiated reversible addition-fragmentation chain-transfer polymerization	Excellent ocular tissue compatibility, effectiveness against postoperative complications	Residual lens epithelial cells (LECs)	[96]
Poly(acrylic acid)-bacterial cellulose membrane	Poly(acrylic acid) brushed onto bacterial cellulose membrane / Reversible addition-fragmentation chain-transfer polymerization	Bone tissue regeneration	Human periodontal ligament stem cells (hPDLSCs)	[97]
Polycarboxybetaine	Zwitterionic brush / Activator regenerated by electron transfer-atom transfer radical polymerization (ARGET-ATRP)	Excellent blood compatibility reduction in the rate of hemolysis, increased resistance to protein adsorption and platelet adhesion	Blood platelets	[98]

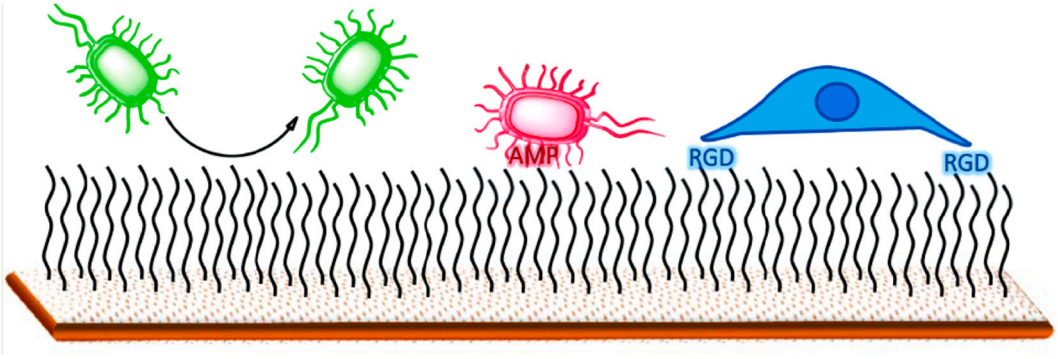

Fig. 24. Functional bioactive polymer brush surface PF127 conjugated with AMP, RGD [15].
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covered with zwitterionic pSBMA brushes. It also considerably improved the binding affinity of surface apatite minerals to the metallic substrate. This approach to surface modification with pSBMA brush-type polymer can be used to produce multifunctional surface coatings, improving metallic implant performance in skeletal tissue engineering, orthopedic and dental care [94].

Gao et al. synthesized non-toxic antimicrobial, biofilm resistant, antimicrobial peptide (AMP) immobilised poly(*N*,*N*-dimethyl acrylamide) / poly(*N*-(3-aminopropyl) methacrylamide) (PDMA / PAPMA) brushes with SI-ATRP technique. We see that representation of peptide immobilised copolymer brush on surface and comparison of ATR-FTIR spectra of peptide immobilised copolymer brush on titanium surface with peptide alone and unmodified copolymer brush in Fig. 27. Synthesized brushes were tested *in vivo* (rat studies). Synthesized multifunctional PDMA / PAPMA brush is thought to have significant potential for developing implants resistant to tissue infection [95].

Han et al. applied zwitterionic poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) polymer brushes on the hydrophobic intraocular lens (IOL) with RAFT polymerization initiated on the surface. *In vivo* (performed on rabbit eye) studies have observed that the biological adhesion of lens epithelial cells or bacteria was effectively reduced in the PMPC brush-modified group compared to naked IOL. It also demonstrated good *in vivo* biocompatibility and effectiveness against post-operative complications on PMPC brush surfaces [96].

Bacterial cellulose membrane (BCM) has recently been recognised as a next-generation carbohydrate-based nanomaterial with great potential in tissue engineering applications. In the study of Klinthoopthamrong et al., PAA brush grafting on BMCs by RAFT polymerization and subsequent plant-derived recombinant human osteopontin (p-rhOPN) immobilisation were successfully performed. The potential of the obtained new functional PAA brush membrane surfaces to support bone tissue regeneration *in vitro* was evaluated against human periodontal ligament stem cells (hPDLSCs). We see the cell growths in Fig. 28 with the immunofluorescence staining technique. In line with the results obtained, the potential of using the new functional PAA brush membrane structure to support bone tissue regeneration has been

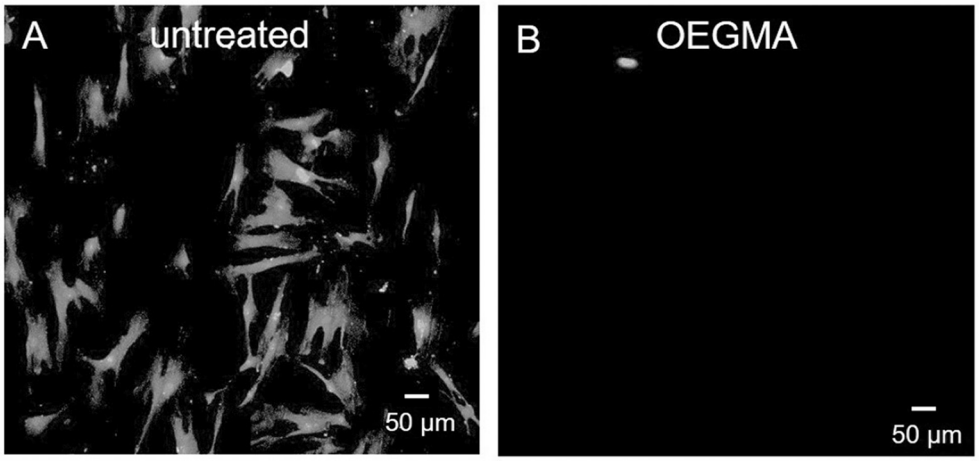

Fig. 25. Poly(OEGMA) brush prevents cell attachment [92].
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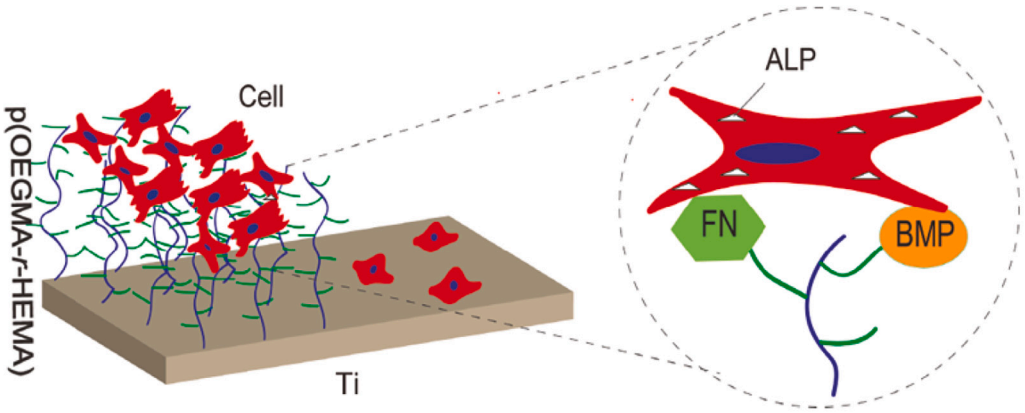

Fig. 26. p (OEGMA-*r*-HEMA) MC3 T3 cell adhesion to brush surface [93].
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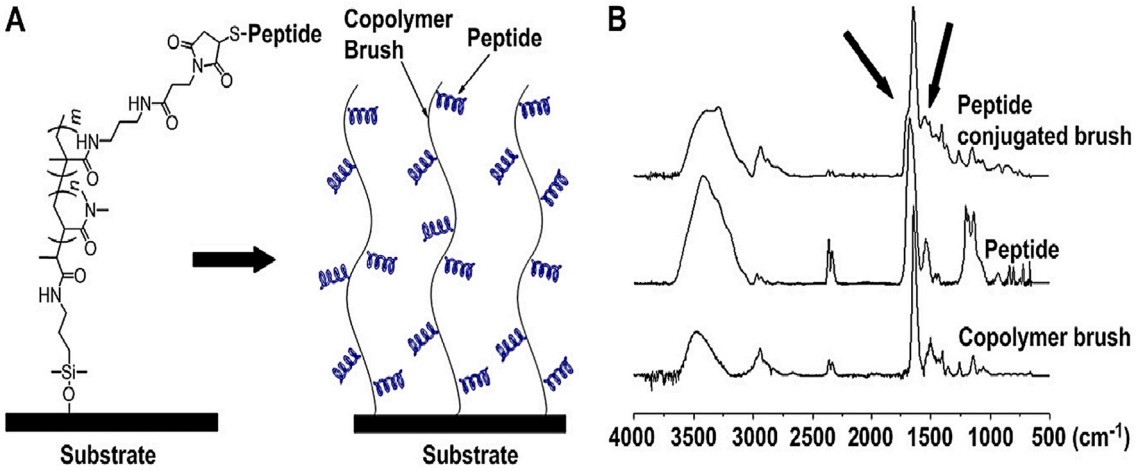

Fig. 27. [A] Representation of peptide immobilised copolymer brush on the surface. [B] Comparison of ATR-FTIR spectra of peptide (Tet-20) immobilised copolymer brush on titanium surface with peptide alone and unmodified copolymer brush [95].
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emphasized [97].

In the study of Wang et al., zwitterionic carboxybetaine brushes were successfully grafted onto cellulose membranes at different polymerization times using the ATRP electron transfer mediated re-generated activator (ARGET-ATRP) method. Blood biocompatibility is generally thought to be related to protein adsorption. Therefore, the

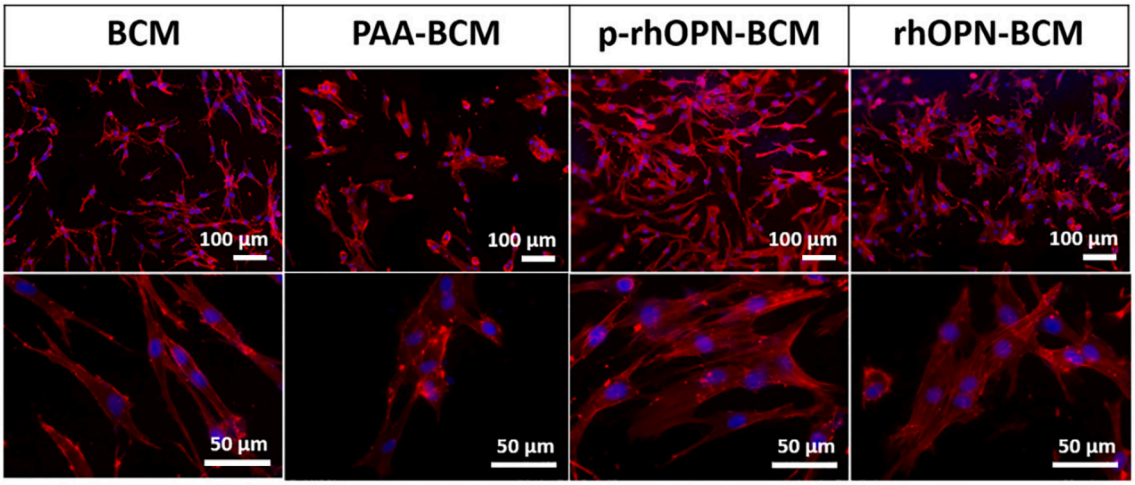

Fig. 28. Immunofluorescent staining pattern of hPDLSCs adhered on the BCM, PAA-BCM, p- rhOPN-BCM and rhOPN-BCM [upper row: scale bar = 100 µm (100×); lower row: scale bar = 50 nm (400×), The p-rhOPN-BCM/rhOPN-BCM for this investigation was covered with p-rhOPN/rhOPN-BCM at approximately 3.86–7.72 ng/cm^2. Images shown represent those seen from at least 3 such fields of view per sample and 3 independent samples [97].
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blood biocompatibility of cellulose membranes functionalised with zwitterionic carboxibetaine brush was evaluated by *in vitro* protein adsorption and platelet adhesion tests. They concluded that the membrane functionalised with the prepared zwitterionic carboxibetaine brush has better blood compatibility than the plain membrane; in other words, it has a reduced hemolysis rate. In conclusion, the study investigated the relationship between the effects of polymerization time of zwitterionic carboxybetaine brushes on the properties of cellulose membrane substrates and protein adsorption and platelet adhesion. The study will contribute to blood-tissue relational research [98].

2.4. Other applications of brush type polymer in tissue engineering

Brush-type polymers are widely used in tissue engineering. In addition to these uses, they are easily used in many biomedical applications due to their active surface area, biocompatibility, adjustable surface properties, and high functionality. Brush-type polymers are used in many areas such as smart materials, biosensor applications, drug release systems, membrane applications, antibacterial surfaces, anti-fungal surfaces or antifouling systems in tissue engineering, apart from the important applications described above [99–135]. Some of the other biomedical applications of brush-type polymers are listed in Table 4.

An important issue in tissue engineering applications is the separation of the cell line grown on a surface from this surface. This is not easy for cells that need a surface to grow on. However, this difficulty can be overcome by using some smart polymer brush structures.

In some smart polymer brushes, the brush structure may change with an external effect [99–105]. In this way, the cell-binding ability of the surface can be changed so that the cell line grown on the surface can be easily separated from the surface (Fig. 29). Especially in brushes carrying azo groups that can change some morphology, the brush structure can vary from a linear structure to mushroom type with an external stimulus. In systems having azo groups, this change is achieved by the change of the azo group from the trans position to the cis position with radiation at a certain wavelength. In some brushes, the morphology of the brush structures can be changed with chemicals or solvents added from the outside. Such properties have led to an increase in the importance of polymer brushes in tissue engineering applications.

Brush-type polymers are a convenient method for preparing controllable and adjustable surfaces. For this reason, brush-type polymer structures are used successfully in many biomedical fields. They are frequently preferred in applications such as obtaining antibacterial, anti-fungal, anti-fouling surfaces or preparing surfaces where some drugs are released in a controlled manner. Another important application area where brush type polymers are preferred in the field of biomedical and tissue engineering is the preparation of antioxidant systems. Dao et al. in their study, synthesized PEG brush polymers containing trisulfide as H_2S donors to improve cellular oxidative stress. Using an amperometric technique, released HS and total sulfur release were found to depend on the concentrations and chemical nature of the trigger molecules (glutathione and cysteine). More importantly, on the location of the reactive groups within the brush structure. In particular, two macromolecular donors, which have the same proportion (30%) as the HS donating monomer but differ in their release moiety location, show similar cellular HS release kinetics when administered to cells at well tolerated doses. These donors can restore reactive oxygen species levels to baseline values when polymer-pretreated cells are exposed to exogenous oxidants (H_2O_2). The study offers a new direction in the preparation of H_2S macromolecule donors and their applications in inhibiting cellular oxidative cascades [124]. Qiu et al. modified cerium oxide nanoparticles with negatively charged poly(3-sulfopropylmethacrylate) and positively charged poly(2-(methacryloyloxy)ethyl-trimethylammonium chloride) polymer brushes by the ATRP technique. It was observed that the polymer brush on the surface of the NPs inhibited oxygen binding and the redox between Ce^{3+} and Ce^{4+} varied to some extent, but the antioxidant capacity of the NPs was still preserved compared to the untreated cells [125]. Chen et al. synthesized TA/PEtOx/Hep functionalized poly(ether sulfone) (PES) hemodialysis membrane containing tannic acid, which combines the high biocompatibility of ringed poli(2-etil-2-oksazolin) (PEtOx) brushes with the anticoagulant property of heparin (Hep) in suppressing oxidative stress for hemodialysis treatment. The functionalized membrane directly increased serum total antioxidant capacity and suppressed lipid peroxidation and protein glycosylation. TA/PEtOx/Hep functionalized hemodialysis membrane effectively protected cardiomyocytes (H9C2) and vascular endothelial cells (HUVEC) from oxidative damage [126].

Brush-type polymers are sometimes used to protect some particular surfaces from bacteria or fungi. Furthermore, brush-type polymers can protect important surfaces and prevent the attachment of some organisms. Antibacterial or antifungal surfaces can be produced, especially with brush structures or brush load characteristics. In this sense, structures or surfaces with similar properties can be obtained by absorbing antibacterial or antifungal molecules between the brush structures.

Madkour and colleagues showed that poly(butylmethacrylate)-*co*-

Table 4
Other applications of brush type polymers in biomedical application.

Polymer structure	Polymer morphology	Application area	Ref.
Magnetic iron oxide-poly(itaconic acid)-poly(acrylic acid)-chitosan	Magnetite nanocomposite brushes	Smart Materials	[99]
Poly(ethylene oxide)	Polymer brushes	Smart Materials	[100]
Poly(*N*,*N*-dimethylaminoethylmethacrylate)-*g*-poly(ε-caprolactone)	Polymer brushes	Smart Materials	[101]
Poly(acrylic acid)	Polymer brushes	Smart Materials	[102]
Poly(n-butyl methacrylate) or poly(n-butylacrylate)	Polymer brushes	Smart Materials	[103]
Poly(methacrylic acid)	Polymer brushes	Smart Materials	[104]
Poly(3-(1-(4-vinylbenzyl)-1-H-imidazol-3-ium-3-yl)propane-1-sulfonate)	Polymer brushes	Smart Materials	[105]
Poly(ethylene glycol) methyl ether methacrylate	Polymer brushes	Drug Delivery	[106]
Doxorubicin-polynorbonene-cholesterol/poly(ethylene glycol)	Brush-like block copolymers	Drug Delivery	[107]
Polyethylene glycol	Polymer brushes	Drug Delivery	[108]
Poly(oligo(ethylene glycol) monomethylether methacrylate-*co*-G3-C12)-g poly(e-caprolactone)	Polymer brushes	Drug Delivery	[109]
Poly(2-hydroxyethyl methacrylate-*g*-poly(ε-caprolactone)-disulfide link-poly(oligoethyleneglycol methacrylate)	Polymer brushes	Drug Delivery	[110]
Poly(β-amino esters)-*g*-cholesterol)-*b*-poly(ethylene glycol)-*b*-(poly(β-amino esters)-*g*-cholesterol)	Polymer brushes	Drug Delivery	[111]
Poly(acrylic acid-*co*- acryl amide)/ Poly(acrylic acid-*co*-methylene bisacrylamide)	Copolymer brushes	Membrane applications	[112]
Polynorbonene-cholesterol/poly(ethylene glycol)	Block copolymer brushes	Membrane applications	[113]
Poly(3-carbamoyl-1-(*p*-vinylbenzyl)pyridinum chloride)	Polymer brushes	Membrane applications	[114]
Poly(ethylene glycol)	Polymer brushes	Membrane applications	[115]
Poly (3-(dimethyl (4-vinylbenzyl) ammonio) propyl sulfonate)	Polymer brushes	Antibacterial surfaces	[116]
Poly-(*N*,*N*-dimethylacrylamide-*co*-*N*-(3-aminopropyl)-methacrylamide hydrochloride)	Polymer brushes	Antibacterial surfaces	[117]
Poly(*N*-hydroxyethyl acrylamide)/poly(trimethylamino) ethyl methacrylate chloride	Polymer brushes	Antibacterial surfaces	[118]
Poly(*N*-isopropylacrylamide) and poly(acrylic acid)	Polymer brushes	Biosensing applications	[119]
Poly(*N*,*N*-dimethylaminoethyl methacrylate) and poly(tert-Butyl methacrylate)	Copolymer brushes	Biosensing applications	[120]
Grafted hydrophilic polymer chain of antimicrobial peptides	Polymer brushes	Biocompatible coating	[121]
Poly(4-vinyl pyridine) functionalized with Os-complex	Polymer brushes	Bioelectronic Applications	[122]
Poly(4-vinylpyridine), poly(4-vinylpyridine-*co*-oligo(ethylene glycol)ethyl ether methacrylate) and poly(oligo(ethylene glycol)ethyl ether methacrylate)	Polymer brushes	Optic Applications	[123]
Trisulfide-Bearing PEG Brush Polymers	Binary mixed brushes containing polymer	Antioxidant	[124]
Poly(3-sulfopropylmethacrylate) and poly(2-(methacryloyloxy)ethyl-trimethyl ammonium chloride)	Polymer brush engineered CeO_2 nanoparticles	Antioxidant	[125]
Tannic acid/poly(2-ethyl-2-oxazoline) (PEtOx) /Heparin functionalized poly(ether sulfone)	Tannic acid, looped PEtOx brush membrane	Antioxidant	[126]
poly(butylmethacrylate)-*co*-poly(Boc-aminoethyl methacrylate)	Polymer brushes on silicon wafers and glass surfaces	Antibacterial surface	[127]
Poly(2-(2-methoxyethoxy)ethyl methacrylate-*co*-hydroxyl-terminated oligo(ethylene glycol) methacrylate)	Polymer brushes incorporating peptide	Antibacterial surface	[128]
Cross-linked poly(*N*-(2-methyl-1-(4-methyl-2,5-dioxoimidazolidin-4-yl)propane-2-yl)acrylamide) and poly(hydantoin acrylamide)	Cross-linked polymer brushes	Antibacterial surface	[129]
Poly 2-(dimethyl amino) ethyl methacrylate (PDMAEMA)	PDMAEMA brushes were decorated on SiO_2 nanoparticles	Antifungal surface	[130]
Allyl glycidyl ether polymer brush	Polymer brushes on polydimethylsiloxane	Antifungal surface	[131]
Poly(ethylene oxide)	Polymer brushes on glass	Antifungal surface	[132]
Poly(carboxybetaine methacrylate), poly(sulfobetaine methacrylate) and poly((2-(methacryloyloxy) ethyl)phosporylcoline)	Zwitterionic polymer brushes	Antifouling surface	[133]
Poly(2-perfuorooctylethyl methacrylate)	Fluoropolymer brush on Si(111)	Antifouling surface	[134]
Poly[(ethylene oxide)-*co*-(ethylene carbonate)]	Polymer brushes on sensor surface	Antifouling surface	[135]

poly(Boc-aminoethyl methacrylate polymer brushes can be highly antimicrobial and kill 100% of *S. aureus* and *E. coli* in less than 5 min. However, its antibacterial ability was independent of polymer layer thickness and density [127]. Glinel et al. functionalized poly(MEO2MA-*co*-HOEGMA) brushes with magainin I, a natural antibacterial peptide, to prepare effective antibacterial coatings. The antibacterial activity of functionalized brushes was successfully tested against two different strains of gram-positive bacteria (*Listeria ivanovii*, *Bacillus cereus*) [128]. In a study by Kinali-Demirci, cross-linked polymer brushes (*N*-(2-hydroxypropyl)methacrylamide) (HPMA) containing *N*-halamine were synthesized to overcome microbial contamination. Using a bifunctional crosslinker, the cross-linked polymer brushes with different N-halamine ratios were synthesized by *in-situ* cross-linking methods with reversible addition fragmentation chain transfer (RAFT) polymerization. The study showed that approximately 94% of *Escherichia coli* and 91% of *Staphylococcus aureus* bacteria in contact with the active cross-linked polymer brushes were killed. It was emphasized that versatile cross-linked polymer brushes containing *N*-halamine have great potential for antibacterial surface applications in many different fields, especially in industrial [129].

Piroonpan et al. prepared silica nanoparticles- vinyltrimethoxysilane- poly 2-(dimethyl amino) ethyl methacrylate (SiO_2 NPs-VTMS-PDMAEMA) brushes by electron beam-induced graft polymerization with the pre-irradiation approach. AgNPs with a diameter of 6 ± 2 nm were successfully produced using the electron beam-induced reduction reaction on the SiO_2NP-VTMS-PDMAEMA surface. SiO_2NP-VTMS-PDMAEMA-AgNPs exhibited the ability to inhibit the growth and expansion of building fungi, *i.e.*, *Syncephalastrum racemosum* and

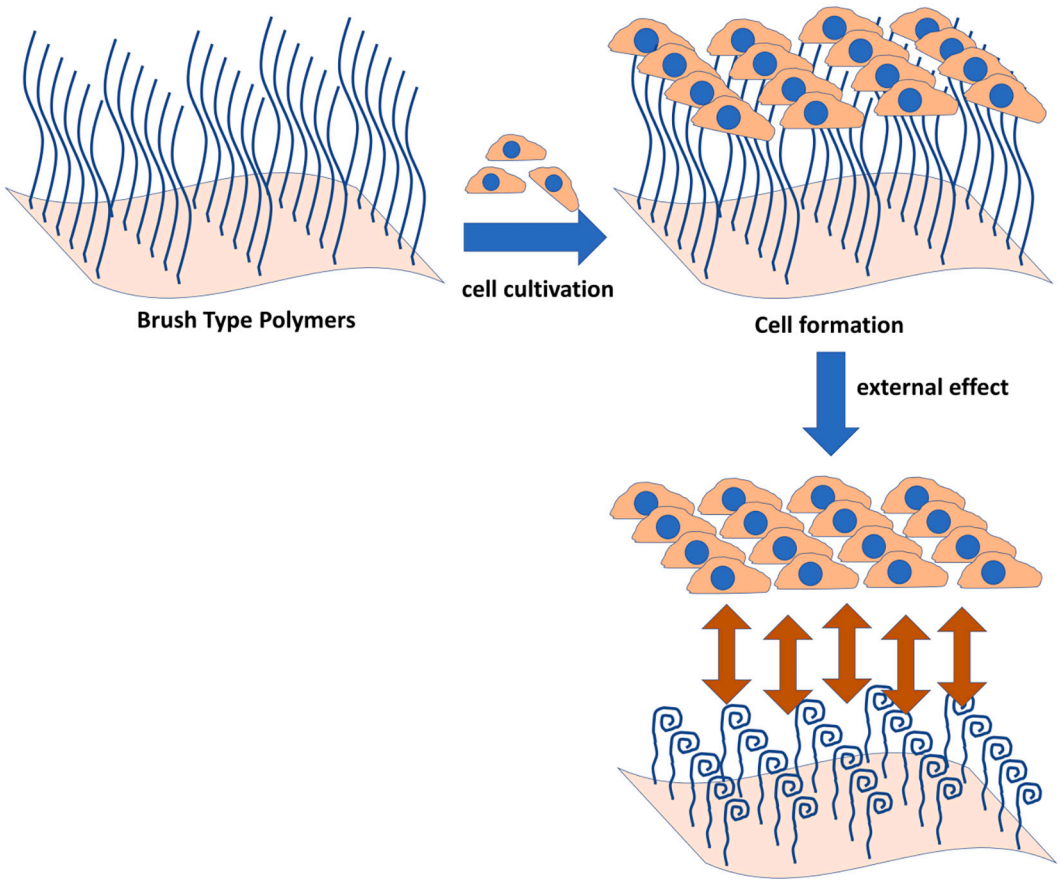

Fig. 29. Cell growing or cell layer creation with smart brush type polymer structures.

Aspergillus niger, with the inhibition zones of 28.3 ± 0.9 mm and 14.1 ± 0.8 mm, respectively [130]. Li et al. developed polydimethylsiloxane-allyl glycidyl ether brushes (PDMS-AGE-RK1, PDMS-AGE-RK2) functionalized with the antimicrobial peptides AMP (peptides RP1 and RK2). They observed that the developed brushes killed *C. albicans* fungal cells. They stated that these synthesized brush structures will contribute to the prevention of fungal infection, which is one of the catheter-related infections [131]. Roosjen et al. synthesized poly(ethylene oxide)-brushes. Antifungal properties of this brushes were determined in *Candida albicans* and *Candida tropicalis* yeast species [132].

Liu et al. revealed that the three zwitterionic brushes [poly(carboxybetaine methacrylate), poly(sulfobetaine methacrylate), and poly((2-(methacryloyloxy)ethyl) phosporylcoline)] exhibit stronger interactions with water molecules and higher surface resistance to a protein than the PEG brush. It was concluded that both the carbon gap length between the zwitterionic groups and the nature of the anionic groups have a marked effect on the antifouling performance, leading to the antifouling ordering of pCBMA > pMPC > pSBMA [133]. Wang et al. synthesized poly(2-perfluorooctylethyl methacrylate) brushes. Antifouling performance can be restored when these brushes are damaged by heating the paint above the glass transition temperature of 40 °C [134]. Cao et al. synthesized poly[(ethylene oxide)-*co*-(ethylene carbonate)] (PEOC) brushes. POEC polymeric brushes exhibit self-renewal properties through gradual hydrolytic cleavage of ethylene carbonate (EC) groups and antifouling properties thanks to ethylene oxide (EO) units. They stated that such a biomimetic polymer brush would have great potential against biofouling in the seas [135].

3. Future perspectives and challenges

Brush-type polymers have become an important focus of polymer research in recent years, with the polymer types used, chain lengths, brush sizes, brush densities and changeable physicochemical properties, ease of synthesis, and ability to change surface properties. There are various reviews on brush-type polymers. For example, Keating et al. reviewed the basics and applications of brush-modified polymer membranes in their review. Keating et al. examined it with an emphasis on adjusting the membrane performance by polymer brush grafting [136]. Ayres, in his review, mentioned the applications of polymer brushes in biomaterials and nanotechnology [137]. In their review, Ma et al. explain how to design functional materials with surface grafting polymer brush techniques and what can be done with polymer brushes in the future [91]. In their review, Zdyrko and Luzinov focused heavily on bonding polymer brushes to various inorganic and Polymer substrates using the grafting method [138]. In their review, Kim and Jung summarised polymer brush-based grafting approaches comparing the self-assembled layered-based coating method, in addition to physicochemical characterisation techniques for surfaces such as wettability, hardness/elasticity, smoothness, and chemical composition [35]. Considering all these reviews, our review comprehensively addresses the applications of brush-type polymers in tissue engineering, which has a significant place today. It is different from the previous reviews and contributes to the literature where it is lacking. Shortly, this review on brush type polymers in tissue engineering; in developing cell/stem cell compatible properties and modulating cell/stem cell differentiation on the adapted surface, scaffold emphasises the importance of creating and controlling environments on the implant and membrane surface and making modifications in the tissue depending on the desired properties. Given the recent advances in tissue engineering, polymer brushes offer interesting features for designing dynamically responsive bio-interfaces that direct cellular and bacterial responses [26]. It has been extensively used to control cell adhesion and proliferative behaviour among these

properties. It is important to create smart surface materials in cell adhesion behaviour. In this context, polymer brushes that are sensitive to heat are exciting. When we look at the literature, thermoresponsive PNIPAAm brushes are common in tissue engineering. However, studies show that PNIPAAm polymer brushes can cause cellular cytotoxicity when transitioning from a hydrophilic to a hydrophobic state. Biocompatible poly[2-(2-methoxy ethoxy) ethyl methacrylate] (PMO2MA) and poly(oligo (ethylene glycol) methacrylate) (POEGMA) copolymer brushes have been developed to solve this problem [91,139]. As a result, it is thought that brush-type polymer structures that are biocompatible in tissue engineering and can exhibit adjustable adhesion and separation behaviours towards target cells with their thermoresponsive properties will be more preferred in the future. In addition, it is thought that different and effective polymer brushes can be obtained by modifying the existing polymer brush structures with functional biomolecules such as proteins, peptides and enzymes, and by changing the surface bioactivity and functionality.

Polymer brushes have a significant potential for protecting a surface, adjusting its properties, activating and improving application areas. For this reason, they have been widely used in many fields such as biomedical, medical, electronics and tissue engineering. They can be easily used in the production of active surfaces for sensors, in the production of surfaces capable of controlled drug release, in the production of antibacterial, anti-fungal, anti-fouling structures, in the preparation of smart surfaces or certain surface morphologies. It can be easily used in tissue engineering to grow cells or cell lines. They can even be used in the production of diagnostic kits for the rapid diagnosis of diseases such as COVIT-19 (SARS-CoV-2), FMF, AIDS and some types of cancer by binding anti-body, active groups or some markers to the brush structures. For this reason, it is an essential tool in both biomedical and tissue engineering applications and its importance is expected to increase in many application areas.

4. Conclusion

As a result, brush-type polymers are widely used in tissue engineering applications for three different purposes. These purposes are to grow cells or create cell layers, prevent cell or microorganism adhesion (antifouling effect), and create a biocidal effect. To create these different effects, the structure of the brush groups on the polymer surface is changed. For example, zwitterionic polymer brushes or groups that prevent cell adhesion are used for the antifouling effect. Using brush structures in brush-type polymers allows applications such as cell recruitment, adhesion, spreading, motility, matrix deposition, proliferation, and differentiation to perform efficiently. Due to these advantages, brush-type polymers are a widely used tool in tissue engineering. This review article reveals the properties, types, purposes, and advantages of brush-type polymers in the field of tissue engineering.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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