Natural Polymer Nanofibrous Scaffold

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Nanofibrous scaffolds mimicking artificial extracellular matrices provide a natural environment for tissue regeneration owing to their large surface area, high porosity, and appreciable drug loading capacity. Electrospun nanofibrous scaffolds have demonstrated promising potential in bone tissue regeneration using a variety of nanomaterials. Natural and synthetic polymeric nanofibrous scaffolds are extensively inspected to regenerate bone tissue. Bone tissue engineering (BTE) procedures make usage of various scaffolds (e.g., composite scaffolds, nanofibrous scaffolds, porous scaffolds, hydrogel scaffolds) in conjunction with biological materials.

bone tissue regeneration nanofibrous scaffolds electrospinning

1. Gelatin

Gelatin (Gel) is a polynucleotide-based biopolymer obtained from animals, bones, tissues, and ligaments. It is regarded as an excellent biomaterial because of its low cost, biodegradability, and biocompatibility. RGD (arginine–glycine–aspartic acid) is the peptide sequence present in gelatin and it helps in cell adherence, growth, and migration of BMSC (bone marrow stromal cells) [1]. Gel's properties have enticed several researchers to use it as a bone regeneration material; however, Gel decomposes quickly and has a low mechanical strength. Crosslinking, which can be conducted physically or chemically, can improve its mechanical properties [2]. In comparison to non-crosslinked scaffolds, electrospun Gel scaffolds that are crosslinked by genipin featured a diameter of 570 ± 140 nm and a stronger fiber structure, with confined fused patches where fibers intersected [3]. Gel as a natural biopolymer was eventually used to create a variety of drug delivery methods, including microparticles, nanoparticles, nanofibers, and hydrogels [4][5]. Nanoparticles of Gel are more effective for drug delivery to bone disease. Gel has versatile qualities as a drug delivery transporter because of its water absorbent and water-soluble properties [6]. Many bioactive compounds, such as HA nanoparticles, have been encapsulated in Gel to enhance osteoconductivity. BSA (bovine serum albumin) has been used as an exemplary protein drug, with a Gel concentration of 0.1% to 0.4%, resulting in a Gel solution with tremendous promise in BTE [7]. Gel-based electrospun nanofibers were shown to effectively initiate osseointegration and fast tissue development, in critical-sized bone damages. Xu et al. demonstrated a nanofibrous scaffold of Gel/β-TCP, wherein Ca^{2+} ions produced from β-TCP can cling to the carboxyl units of the Gel molecular chain, resulting in ionic-type interactions which stimulate osteoblast growth. Electrospun nanofibrous Gel/β-TCP has been demonstrated to have excellent biocompatibility and aid in the repairing of bone defects [8]. Salifu and colleagues examined the consequence of human embryonic osteoblast cells on crosslinked electrospun Gel/HA-aligned fiber scaffolds with varying HA contents [9]. Because of its qualities as a natural biomaterial and history of safe usage, Gel has been extensively

researched as a drug delivery transporter across numerous drug groups in a varied range of medical and therapeutic uses [10].

2. Silk Fibroin

SF (silk fibroin) is a bio-macromolecule of protein complex [11][12]. It has been utilized as a biomaterial in the form of thin films, 3D scaffolds, electrospun fibers, hydrogels, and spheres in several biomedical applications, including BTE. SF-based nanoparticles are appealing in the study of drug delivery owing to their biocompatibility, nontoxicity, flexibility, elasticity, improvement of cell attachment and growth, chemical modification role, microbial resistance, low inflammatory response, and crosslinking capability [13]. Because of these characteristics, SF is the most reliable material in BTR. Membranes, microspheres, hydrogels, porous scaffolds, and nanofibers can all be fabricated from SF [14]. In the area of tissue defect rejuvenation, SF electrospun scaffolds are extensively researched for bone, brain, subcutaneous, etc. SF, as a biomaterial for BTR, not only induces ECM and is compatible with cells, but it may also stimulate the formation of HA crystals, which leads to the integration of bone. SF, being an osteogenic biomaterial, has the capacity to promote stem cell development by blocking the Notch pathway [15]. Kirker-Head and co-workers fabricated silk scaffolds that have been proven to be an osteoconductive mold for repairing critical size mid-femoral segment deformities in nude rats [16]. The use of SF to deliver BMP-2 to be used in bone regeneration has been extensively researched. In vivo, SF mixed with BMP-2 growth factors and HMSCs (human mesenchymal stem cells) improved osteoblastic adhesion and differentiation, increased ALP staining, and encouraged bone growth [17]. SF is typically used in concert with other biomaterials that have been shown to assist BTR, such as inorganic components consisting of calcium phosphate or collagen, both of which are naturally present in bone [18]. In a rabbit model, the fusion of HA nanoparticles into silk matrix improved bone repair [19]. In vitro bone regeneration was achieved using electrospun SF/PLCL nanofibrous scaffolds cultured with hADSCs. The tensile strength of the SF/PLCL (50/50) scaffold was (6 MPa). Furthermore, the aptitude of Silk fibroin to indorse osteogen differentiation of the hADSCs (human adipose-derived mesenchymal stem cells) was proven by its elevated ALP activity, which had an absorbance index with value of 150 when matched to pure PLCL (with an absorbance index of 80) [3].

3. Collagen

Collagen (Col) is a biocompatible and bioactive polypeptide molecule that represents about 25% to 35% of the complete body protein and has a characteristic molecular structure and fibrillar structure. It helps support extracellular scaffolding, which represents a significant component of ECM in numerous connective tissues, including bone [20][21]. Col is a category of naturally occurring proteins that make up the majority of connective tissue. Col-I is the utmost prevalent kind of collagen in the human body. Col-I is biodegradable, antigenic, and has beneficial properties such as angiogenesis stimulation and prevention, along with improved cellular proliferation as well as differentiation promotion. Due to these qualities, Kumar et al. proposed that Col has become a new preferred substrate material for a variety of bio-degradable tissue engineering and regenerative medicine applications. These researchers created a multilayer nanocomposite of nHA-Col to examine the influence of Col.

The results showed that scaffold specimens improved seeded MSC adhesion, growth, and differentiation [22][23]. Col scaffold enhanced cell growth in vivo [24]. Because of its safety and biocompatibility, Col-based drug delivery scaffolds are commonly utilized as templates to stimulate bone regeneration. Col-derived scaffolds created through electrospinning have a 3D microstructure that can be employed to induce tissue regeneration effectively. Fischer et al. created Col/HA scaffolds that may be exploited in tissue engineering scaffolds to stimulate cell development and enhance cellular adhesion [25]. A permeable Col-based scaffold was treated with Sulfo-SMCC (Sulfosuccinimidyl-4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate) and Traut's reagent to increase BMP-2 adhesion to Col scaffolds. BMP-2 release slowed by crosslinking, but its biological activity was not affected. In the in vivo investigation, the use of Sulfo-SMCC and Traut's reagent to chemically link Col scaffolds with BMP-2 was found to be an excellent delivery approach for bone development and BTE [26]. To assess osteointegration, cell adhesion, propagation, and differentiation were assessed in Col-I/PLLA and HA-modified scaffolds. The results reveal that a segmental bone defect may be repaired 8 weeks after surgery utilizing nHA/Col/PLLA reinforced with chitin fibers and seeded with cultured goat bone marrow MSCs [27].

4. Chitosan

Chitosan (CS) is a polysaccharide class of biopolymers that consists of a β-(1-4)-linked 2-amine-2-deoxy-β-d-glucose monomeric parts. CS is normally gained by deacetylation of the chitin that is derivative of fungus cell walls, arthropod and insect exoskeletons, mollusk radulae, and cephalopod beaks. Because of its admirable traits such as high charge density and being biocompatible, biodegradable, non-toxic, antimicrobial, non-carcinogenic, and simple to make, it was investigated as a factor in drug delivery applications in tissue engineering and pharmaceutics [28][29]. Some studies have shown that CS improves cell adhesion, proliferation, osteoblast differentiation, and mineralization. This activity is linked to the scaffold's physical properties as well as electrostatic interactions (caused by CS's cationic nature) with a variety of chemicals, including cytokines and GFs. These substances help cells colonize more effectively [30][31].

However, pure CS has weak mechanical properties, lacks osteogenic inductivity, and lacks natural bone properties. To overcome this limitation, CS scaffolds can be combined with other natural or artificial macromolecules (alginate, Gel, Col, SF, PVA, PCL, PVP, etc.) and biomaterials (β-tricalcium phosphate, SiO_2, HA, etc.). Calcium phosphate particles and HA nanoparticles could be mixed with CS matrix to create CS-based composites that imitate real bone. The qualities predicted for CS/calcium phosphate scaffolds include biocompatible, biodegradability, osteoconductive, antimicrobial properties, osteoinduction, angiogenesis control, and mechanical strength. Several investigations using CS/HA composite materials for BTR have been accomplished [32][33]. Zhang et al. found that when nHA/CS composite scaffolds are placed into the segmental bone lesion, the bone regeneration rate is greater than pure CS scaffolds. For the investigation, critical-sized bone defects (length: 10 mm, diameter: 6 mm) were fashioned in the left femoral condyles of 43 healthy New Zealand white rabbits. The femoral condyle deficiencies were treated with nHA/CS scaffold implantation, pure CS implantation, or left unfilled. The data show that 12 weeks following the treatment, full repair of the segmental bone defect was seen in rabbits implanted with the nHA/CS scaffold, whereas the defect remained visible in the CS-only group [34]. Composite of HA/CS may also be employed

as a functional coating on further implants to develop biomaterials with outstanding osteoinduction capabilities. Wang et al. investigated that a coating of HA/CS on a titanium surface is a favorable approach for producing biomaterials with improved osteointegration potential and tested it in diabetic patients. The histological analysis at the bone–implant interface demonstrated that after four weeks, tiny regenerating bone was incorporated into Ti/cTi. After twelve weeks, greater bone contact was detected, plus a greater volume of new bone formed in the cTi implant compared to the Ti implants. CS could be layered on top of metal (Ti) implants to increase osteointegration [35]. Sharifi et al. created a CS/PCL composite scaffold and then conducted an MTT experiment using human osteoblast (MG-63) cells to assess its cell proliferation. The result demonstrated that scaffolds are biocompatible, promoting proliferation, and can be an outstanding contender for BTE application [36]. Chen et al. used coaxial electrospinning to create Gel–CS/HA core-shell nanofibrous scaffolds. Inside the core-shell nanofibrous scaffold, CS and Gel promote cell attachment and proliferation, which is aided even more with the existence of HA deposition on the surfaces of nanofiber. When equated to CS, Gel, and CS–Gel composite nanofibers, core-shell CS–Gel nanofiber scaffold boosted HA mineralization efficacy and designed a homogeneous HA deposit. The results of an MTT experiment using human osteoblast (MG-63) cells cultivated on core-shell nanofibers reveal that HA deposition on the core-shell CS–Gel nanofibers may also promote osteoblast cell growth [37]. CS and alginate can be mixed to form a polyelectrolytic complex that results in mutual precipitation and increased mechanical strength. CS provides structure to the supports, whereas alginate aids cell regeneration [38].

References

1. Cheng, N.; Jeschke, M.G.; Sheikholeslam, M.; Datu, A.K.; Oh, H.H.; Amini-Nik, S. Promotion of dermal regeneration using pullulan/gelatin porous skin substitute. J. Tissue Eng. Regen. Med. 2019, 13, 1965–1977.
2. Adithya, S.P.; Sidharthan, D.S.; Abhinandan, R.; Balagangadharan, K.; Selvamurugan, N. Nanosheets-incorporated bio-composites containing natural and synthetic polymers/ceramics for bone tissue engineering. Int. J. Biol. Macromol. 2020, 164, 1960–1972.
3. Nemati, S.; Kim, S.-J.; Shin, Y.M.; Shin, H. Current progress in application of polymeric nanofibers to tissue engineering. Nano Converg. 2019, 6, 36.
4. Foox, M.; Zilberman, M. Drug delivery from gelatin-based systems. Expert Opin. Drug Deliv. 2015, 12, 1547–1563.
5. Zhang, Y.; Ouyang, H.; Lim, C.T.; Ramakrishna, S.; Huang, Z.-M. Electrospinning of gelatin fibers and gelatin/PCL composite fibrous scaffolds. J. Biomed. Mater. Res. 2005, 72, 156–165.
6. Lien, S.-M.; Ko, L.-Y.; Huang, T.-J. Effect of pore size on ECM secretion and cell growth in gelatin scaffold for articular cartilage tissue engineering. Acta Biomater. 2009, 5, 670–679.
7. Song, R.; Murphy, M.; Li, C.; Ting, K.; Soo, C.; Zheng, Z. Current development of biodegradable polymeric materials for biomedical applications. Drug Des. Dev. Ther. 2018, 12, 3117–3145.

8. Xu, M.; Zhang, X.; Meng, S.; Dai, X.; Han, B.; Deng, X. Enhanced Critical Size Defect Repair in Rabbit Mandible by Electrospun Gelatin/β-TCP Composite Nanofibrous Membranes. J. Nanomater. 2015, 2015, 396916.
9. Salifu, A.A.; Lekakou, C.; Labeed, F.H. Electrospun oriented gelatin-hydroxyapatite fiber scaffolds for bone tissue engineering. J. Biomed. Mater. Res. Part A 2017, 105, 1911–1926.
10. Khalf, A.; Madihally, S.V. Recent advances in multiaxial electrospinning for drug delivery. Eur. J. Pharm. Biopharm. 2017, 112, 1–17.
11. Nguyen, T.P.; Nguyen, Q.V.; Nguyen, V.-H.; Le, T.-H.; Huynh, V.Q.N.; Vo, D.-V.N.; Trinh, Q.T.; Kim, S.Y.; Van Le, Q. Silk Fibroin-Based Biomaterials for Biomedical Applications: A Review. Polymers 2019, 11, 1933.
12. Malafaya, P.B.; Silva, G.A.; Reis, R.L. Natural–origin polymers as carriers and scaffolds for biomolecules and cell delivery in tissue engineering applications. Adv. Drug Deliv. Rev. 2007, 59, 207–233.
13. Kim, U.-J.; Park, J.; Kim, H.J.; Wada, M.; Kaplan, D.L. Three-dimensional aqueous-derived biomaterial scaffolds from silk fibroin. Biomaterials 2005, 26, 2775–2785.
14. Tomeh, M.A.; Hadianamrei, R.; Zhao, X. Silk Fibroin as a Functional Biomaterial for Drug and Gene Delivery. Pharmaceutics 2019, 11, 494.
15. Wang, Z.; Wang, Y.; Yan, J.; Zhang, K.; Lin, F.; Xiang, L.; Deng, L.; Guan, Z.; Cui, W.; Zhang, H. Pharmaceutical electrospinning and 3D printing scaffold design for bone regeneration. Adv. Drug Deliv. Rev. 2021, 174, 504–534.
16. Kirker-Head, C.; Karageorgiou, V.; Hofmann, S.; Fajardo, R.; Betz, O.; Merkle, H.P.; Hilbe, M.; von Rechenberg, B.; McCool, J.; Abrahamsen, L.; et al. BMP-silk composite matrices heal critically sized femoral defects. Bone 2007, 41, 247–255.
17. Sun, W.; Gregory, D.A.; Tomeh, M.A.; Zhao, X. Silk Fibroin as a Functional Biomaterial for Tissue Engineering. Int. J. Mol. Sci. 2021, 22, 1499.
18. Wani, S.U.D.; Gautam, S.P.; Qadrie, Z.L.; Gangadharappa, H.V. Silk fibroin as a natural polymeric based bio-material for tissue engineering and drug delivery systems-A review. Int. J. Biol. Macromol. 2020, 163, 2145–2161.
19. Wang, G.; Yang, H.; Li, M.; Lu, S.; Chen, X.; Cai, X. The use of silk fibroin/hydroxyapatite composite co-cultured with rabbit bone-marrow stromal cells in the healing of a segmental bone defect. J. Bone Jt. Surg. Br. Vol. 2010, 92, 320–325.
20. Dong, C.; Lv, Y. Application of Collagen Scaffold in Tissue Engineering: Recent Advances and New Perspectives. Polymers 2016, 8, 42.

21. Nune, S.K.; Rama, K.S.; Dirisala, V.R.; Chavali, M.Y. Chapter 11—Electrospinning of Collagen Nanofiber Scaffolds for Tissue Repair and Regeneration. In Nanostructures for Novel Therapy: Synthesis, Characterization and Applications; Elsevier Inc.: Amsterdam, The Netherlands, 2017; pp. 281–311.
22. Zhao, F.; Grayson, W.L.; Ma, T.; Bunnell, B.; Lu, W.W. Effects of hydroxyapatite in 3-D chitosan–gelatin polymer network on human mesenchymal stem cell construct development. Biomaterials 2006, 27, 1859–1867.
23. Kumar, B.; Feller, J.-F.; Castro, M.; Lu, J. Conductive bio-Polymer nano-Composites (CPC): Chitosan-carbon nanotube transducers assembled via spray layer-by-layer for volatile organic compound sensing. Talanta 2010, 81, 908–915.
24. Zuber, M.; Zia, F.; Zia, K.M.; Tabasum, S.; Salman, M.; Sultan, N. Collagen based polyurethanes—A review of recent advances and perspective. Int. J. Biol. Macromol. 2015, 80, 366–374.
25. Fischer, R.L.; McCoy, M.G.; Grant, S.A. Electrospinning collagen and hyaluronic acid nanofiber meshes. J. Mater. Sci. Mater. Med. 2012, 23, 1645–1654.
26. Zhang, Q.; He, Q.-F.; Zhang, T.-H.; Yu, X.-L.; Liu, Q.; Deng, F.-L. Improvement in the delivery system of bone morphogenetic protein-2: A new approach to promote bone formation. Biomed. Mater. 2012, 7, 045002.
27. Hao, W.; Dong, J.; Jiang, M.; Wu, J.; Cui, F.; Zhou, D. Enhanced bone formation in large segmental radial defects by combining adipose-derived stem cells expressing bone morphogenetic protein 2 with nHA/RHLC/PLA scaffold. Int. Orthop. 2010, 34, 1341–1349.
28. Funda, G.; Taschieri, S.; Bruno, G.A.; Grecchi, E.; Paolo, S.; Girolamo, D.; Del Fabbro, M. Nanotechnology Scaffolds for Alveolar Bone Regeneration. Materials 2020, 13, 201.
29. Shoueir, K.R.; El-Desouky, N.; Rashad, M.M.; Ahmed, M.K.; Janowska, I.; El-Kemary, M. Chitosan based-nanoparticles and nanocapsules: Overview, physicochemical features, applications of a nanofibrous scaffold, and bioprinting. Int. J. Biol. Macromol. 2021, 167, 1176–1197.
30. Deepthi, S.; Venkatesan, J.; Kim, S.-K.; Bumgardner, J.D.; Jayakumar, R. An overview of chitin or chitosan/nano ceramic composite scaffolds for bone tissue engineering. Int. J. Biol. Macromol. 2016, 93, 1338–1353.
31. Suh, J.-K.F.; Matthew, H.W.T. Application of chitosan-based polysaccharide biomaterials in cartilage tissue engineering: A review. Biomaterials 2000, 21, 2589–2598.
32. Subuki, I.; Adnan, N.; Sharudin, R.W. Biodegradable scaffold of natural polymer and hydroxyapatite for bone tissue engineering: A short review. AIP Conf. Proc. 2018, 2031, 020019.
33. Bhowmick, A.; Banerjee, S.; Kumar, R.; Kundu, P.P. Hydroxyapatite-Packed Chitosan-PMMA Nanocomposite: A Promising Material for Construction of Synthetic Bone. Adv. Polym. Sci. 2013,

254, 135–168.

34. Zhang, X.; Zhu, L.; Lv, H.; Cao, Y.; Liu, Y.; Xu, Y.; Ye, W.; Wang, J. Repair of rabbit femoral condyle bone defects with injectable nanohydroxyapatite/chitosan composites. J. Mater. Sci. Mater. Med. 2012, 23, 1941–1949.
35. Ma, X.-Y.; Feng, Y.-F.; Ma, Z.-S.; Li, X.; Wang, J.; Wang, L.; Lei, W. The promotion of osteointegration under diabetic conditions using chitosan/hydroxyapatite composite coating on porous titanium surfaces. Biomaterials 2014, 35, 7259–7270.
36. Sharifi, F.; Atyabi, S.M.; Norouzian, D.; Zandi, M.; Irani, S.; Bakhshi, H. Polycaprolactone/carboxymethyl chitosan nanofibrous scaffolds for bone tissue engineering application. Int. J. Biol. Macromol. 2018, 115, 243–248.
37. Chen, P.; Liu, L.; Pan, J.; Mei, J.; Li, C.; Zheng, Y. Biomimetic composite scaffold of hydroxyapatite/gelatin-chitosan core-shell nanofibers for bone tissue engineering. Mater. Sci. Eng. C 2019, 97, 325–335.
38. Victor, R.D.S.; Santos, A.M.D.C.; De Sousa, B.V.; Neves, G.D.A.; Santana, L.N.D.L.; Menezes, R.R. A Review on Chitosan’s Uses as Biomaterial: Tissue Engineering, Drug Delivery Systems and Cancer Treatment. Materials 2020, 13, 4995.