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Review Article

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Poly (Lactic Acid) Nano-structures for Cartilage Regeneration and Joint Repair: Strategies and Ideas

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Abstract

Cartilage repair and regeneration remain mainly obstinate owing to a very low regenerative potential of this tissue. The field of Cartilage Tissue Engineering, which is aimed to repair, regenerate, and improve injured or diseased cartilage functionality, has induced penetrating attention and grips inordinate possible for successful Cartilage-Therapy. Improvements in bio-material investigation and High-tech enhanced constructing of scaffolds have improved the productivity of Tissue-Engineering. Nano fibrous scaffolds mimic the native extracellular matrix of cartilage, offering a provision for cartilage tissue engineering through advancing Cell Viability, Cell Adhesion, Cell Propagation, Osteo-genic Isolation, Vascularization, Host Integration, and Load Bearing. Fabrication of these scaffolds with Poly Lactic Acid (PLA) Bio Polymer has permitted modified cartilage repair. PLA is effortlessly processable, degrades and degenerates to natural-metabolites. Consequently, the prospective of using PLA Nano fibers for cartilage repair is a thoughtful objective for researchers in new examinations. In this review, we deliberate the various methodologies applied in constructing PLA Nano-fibrous scaffolds for Cartilage Tissue Engineering. Also a general report of the present state and development in cartilage repair and regeneration by Poly Lactic Acid Nano-fibers will be delivered.

Keywords: Nano fiber; Tissue Engineering; Poly Lactic Acid; Cartilage Repair; Scaffold

Introduction

Cartilage is composed of cells entrapped in a mesh of collagen fibers together with a complex arrangement of other macromolecules like proteoglycans[1,2], that maintain the right volume of water content in the tissue (figure 1)[3-6]. Collagen I is the signature of various connective tissues such as bone, skin, and tendon, whereas collagen II is of hyaline cartilage [2,7,8]. The tissue has a high water content indicating how the interaction between the collagen fibrils and proteoglycans preserves its hydrated state [9,10]. These characteristics contribute to the unique physical properties of cartilage, its lubrication, and the efficiency for oxygen and other nutrients availability via diffusion [8,11,12].The template of the collagen meshwork and the intricacy of the collagenous assembly are very complex[7,8,13-15]. The abundant macromolecules of collagen type II can covalently bind with other types of collagen present in adult human cartilage namely - type III, IX and XI, all of which play a critical part in the tissue remodeling [16,17]. Cartilage is made of hypothetical layers which can be distinguished by their microstructural and physiological differences [18-22]. The thinnest layer of all is the superficial layer and contains flattened chondrocyte cells which are parallel to the articulating surface [23,24]. Any disruption of this layer can alter the cartilage biomechanical properties leading to the development of diseases such as osteoarthritis[25,26]. The superficial layer can act as a membrane inhibiting the entrance of molecules which are larger in size as compared to water molecules, for example, pathogens in order to keep the cartilage safe from the immune system attacks[27-29]. In this zone, chondrocytes are responsible for secreting proteoglycans in high and collagen fibers in low concentration, making it the highest water content region across the cartilage ECM length[30-32].

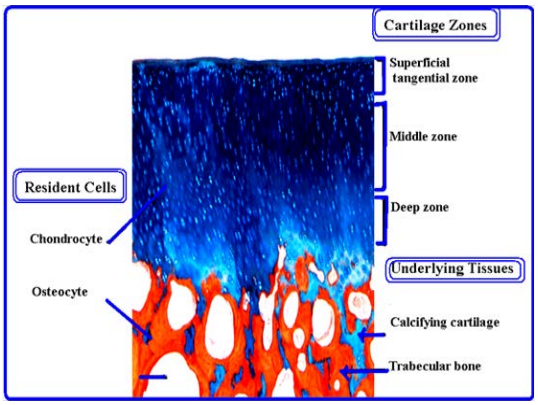

Figure 1. Cartilage section detailing the different zones from the upper superficial zone down to the underlying bone [1].

Articular Cartilage

Repair of the articular-cartilage remains to be mainly obstinate owing to very low reformative characterization of the tissue. The structural composition of articular-cartilage is seen in table 1 [8,9,33-35]

There are 4 regions with various constructions in articular-cartilage figure 2 [36]:

- Superficial-zone
- Middle-zone
- Deep-zone
- Calcified-zone

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Articular-Cartilage		Roles	Ref.
Solid-Phase (ECM)	Collagen	Contributes to tensile specifications and macro-molecule entrapment.	[33]
	Proteoglycan	Contributes to compressive and flow dependent viscoelastic specifications.	[8]
	Other glycoprotein, fibronectin , etc.	Contributes to cell-ECM interaction and the stability of ECM.	[9]
Solid-Phase (Cells)		Modify ECM and maintaining appropriate tissue-size.	[34]
Fluid-Phase		Exchanges nutrients with synovial-fluid, greases the joint, and contributes to compressive-resistance and distortion.	[35]

Table 1. Structural composition of articular-cartilage.

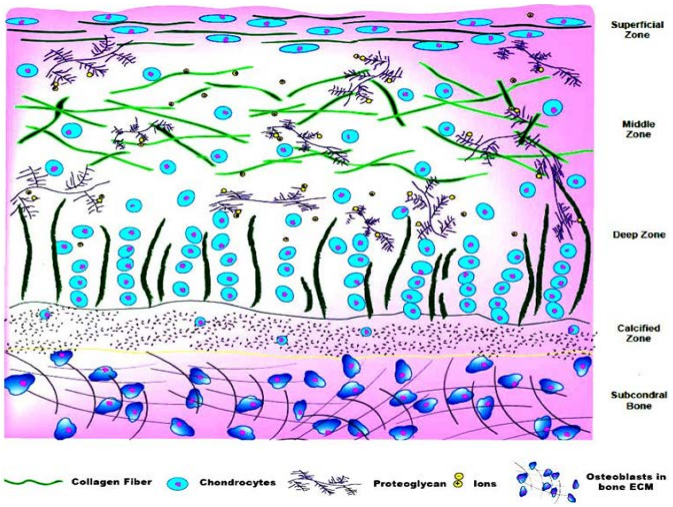

Figure 2. Schematic representation of the arrangement and construction of articular-cartilage [36].

Cell Sources for Cartilage Repair

Cartilage defect is common in clinical but disreputably problematic to treat for low regenerative and migratory capacity of chondrocytes [6,10,37].

Chondrocytes

Chondrocytes the resident cells of cartilage, create elements of extracellular matrix and are cells of option for engineering cartilage [2,19,38]. Adult chondrocytes have been isolated from different resources such as nasal septum, articular cartilage, ribs and ear cartilage [5,25].

Mesenchymal stem cells

Multipotent mesenchymal stromal cells or mesenchymal stem cells (MSC) are important resource of cells for cartilage engineering because of their easy entrance and high capability of *in vitro* growth[31,39,40]. They are chiefly isolated from bone marrow or adipose tissues but have been also isolated from several tissues including periosteum, synovium, umbilical cord vein or placenta[41-43]. Nano-fibrous scaffolds that manufactured from bio-degradable materials have shown a lot of advantages for repairing the cartilage defects in recent years [16,44,45].

Growth factors for Cartilage repair

Cartilage repair or healing is initiated soon after injury and comprised of a cascade of cellular actions wherein mesenchymal cells respond to various regulators and proliferate, differentiate, and synthesize ECM[8,46]. Prevailing concepts propose that growth factors may regulate various phases in this event table 2[1,6,46-49].

Growth-factor	Functioning historical	Purpose
Bone morphogenetic protein (BMP)	Whole process	Induce undifferentiated mesenchymal cells to differentiate into osteogenesis and cartilage
Insulin-like growth factor (IGF)	Bony callus formation	Promote division of cartilage cell proliferation and the synthesis of cartilage matrix
Tumor necrosis factor (TNF)	Fibro-cartilaginous callus formation	Inhibit the synthesis of collagen osteocalcin and collagen synthesis of fibroblasts and cartilage proteoglycan synthesis

Table 2. Functions of growth factors in cartilage repair [1,6,49].

Nano-Fibrous Designs for Mimicking Cartilage

The biomedical knowledge for engineering soft-tissues for repair of cartilage tissues is still evolving [8,38,50]. The strategy of a perfect model for cartilage is difficult in the case of tissue-engineering[30,51]. Certainly, cartilage is a multifaceted tissue accomplished of resisting large compressive masses throughout ordinary actions, it is a soft, flexible, and viscoelastic tissue that covers the bone from outside at joints (articular cartilage), and is present in the ear, rib cage, nose, and other body-components[13,52,53]. There are 3 kinds of cartilage, based on ECM composition: Elastic Cartilage (ECM with elastic fibers), Fibro Cartilage (ECM enriched with collagenous fibers), and Hyaline Cartilage (ECM enriched with glycosaminoglycans [GAGs]) [23,33].Coupling the cells and scaffolds (which is required in cartilage tissue formation) is one of the most important problems for achieving the proper mechanical properties[54,55]. This model should allow chondrogenic proliferation and differentiation and also must hold the new formed ECM within the scaffolds, so that a tissue will be formed that devotedly restructure cartilage morphology and specifications [1,2,20,56].Nano-fibers have been noticed mainly because of their ability for simulating the natural properties of ECM (like fibrous structure and porous shape) [5,13,32]. Typically contrived using electro spinning, such fibers are regularly used as strong reinforcements in Nano composites [7,57-59]. In addition to their ability for mimicking the native extracellular matrix[45,60,61], Nano fibrous scaffolds also exhibit a higher surface to volume ratio[62-66], leading to greater cellular attachment than larger fibers. Furthermore, Nano fiber reinforced composites have been shown to have greater mechanical strength than old style unfilled or carbon glass fiber filled composites, and added a main advantage to scaffolds which need higher mechanical properties [14,67-72]. Ideal scaffold for cartilage regeneration should have respectable surgical-handiness and mechanical-properties (particularly Young's modulus significance) accustomed to the implantation area, e.g., Young's modulus (E) value = 0.4-0.83 MPa for cartilage[50,73]. The progress of Nano-fibrous scaffolds with materials that display strong mechanical support, bio-compatibility, bio-degradability, and osteo-inductive possessions is the basis for cartilage tissue engineering [7,8,13-15,74].

Applications of PLA Nano Structures in Cartilage Regeneration

For the cartilage regeneration, bio-material should not only help for new tissue formation in the location of injury also should keep the injury free from infections which are related to the bio-materials, that might reason extended inflammation[26,75].

Moreover, bio based materials for cartilage regeneration must be more elastic compared to the other scaffolds and do chiefly created by

means of biocompatible polymers [8,16,23,30,75] (Natural or Synthetic) frequently look like those arising in natural cartilage tissue, e.g. Chitosan, Hyaluronic Acid, Collagen, Fibrin, Silk, Alginate, Poly(Lactic Acid)[PLA], Poly(3-Caprolactone) (PCL), or Poly(L-Lactide-co-Caprolactone) (PLCL) [36,76,77].

Poly (Lactic Acid)

PLA is a bio-based, bio-sourced, biodegradable, bio-absorbable, biocompatible polymer[7,78,79], that has helix structure[80,81], with an orthorhombic unit cell [82-84]. Lactic acid (2-hydroxypropionic acid, CH_3–CHOHCOOH) is the monomeric building block of PLA. PLA holds stereo isomers for instance Poly (L-Lactide) (PLLA), Poly(D-Lactide) (PDLA), and Poly(DL-Lactide) (PDLLA) [85-87]. PLA has an extensive variation of bio-medical uses[88], for example sutures, drug delivery vehicles, prosthetics, vascular grafts, bone screws, skin regeneration scaffolds, and pins for fixation[83,89,90]. PLA degrades generally to non-toxic derivatives, also can be simply blended with other materials, spreading its usage [91-93]. PLA is used as a scaffold for renewing cartilage not only because of alike mechanical possessions to the objective tissue, nonetheless furthermore owing to good biological interactions with host cells and when implanted [30]. However, PLA scaffolds may hamper cell seeding because of hydrophobic nature of polymer [7,15,90,94].

Application of PLA Nanostructures in Cartilage Regeneration Filed

For cartilage tissue engineering applications, PLA Nanostructures have been utilized in a vast diversity of forms like multilayer Nano fiber fabrics, porous scaffolds, Nano fibers containing HAP (hydroxyapatite), porous scaffolds combined with growth factors which will be reported in detail in below. Furthermore, functionalization of PLA Nanostructures with treatments in order to introduce bioactive molecules will also be described on the following pages.

Gelatin (GEL) is a bio-degradable and bio-compatible material and a partial derivative of collagen, that is the main element of skin, bone, cartilage and connective tissues[32,39,95]. Researchers regularly use GEL in tissue engineering fields a low cost collagen substitute to support cell adhesion, migration, differentiation and proliferation[13,96,97]. GEL blends with natural or synthetic polymers show physicochemical, biomechanical, and biocompatibility features that are suitable for scaffolds [7,13,39,95,98]. Carbon nano-tubes (CNTs) can modify electrical and mechanical properties of PLA fibers obtained via electro-spinning, this property is necessary when stimulating CARTILAGE TISSUE FORMATION [99].

Researchers in 2018, established a PLA-GEL Resveratrol 3D Nano fibrous scaffold for supporting the treatment of cartilage defect. Resveratrol[12] is a type of durable poly-phenols which have many profits for growing of chondrocytes containing anti-senescence, anti-inflammation, and decreasing the destruction of ECM. They designed a micro fluidic chip-based drug screening expedient for choosing the best concentration of resveratrol, which has durable protecting ability for chondrocyte. A novel PLA-Gelatine 3-D scaffolds which hold resveratrol (a biological factor, strong natural polyphenols with the characteristics of anti-senescence, anti-inflammation, and reducing the damage of extracellular matrix, which could play a similar role in cartilage repair) were manufactured for repairing cartilage injury. The chondrocytes were positively cultured on PLA scaffolds. The results show that this new PLA scaffold can seriously help the cartilage formation figure 3 [7].

A novel Poly (Lactic-co-Glycolic Acid) Hyaluronic Acid Fibrin (45S Bio-active Glass) Nano composite scaffolds seeded with human Adipose-Derived Mesenchymal Stem Cells (hADMSCs) were explored as a hypothesis for therapy of cartilage defects. Assay displayed that addition of Hyaluronic Acid, Fibrin, and 45S-Glass Nanoparticles could adapt the degradation-rate of PLGA. The scaffolds did not show any cytotoxicity, and also hADMSCs were observed attached to the scaffolds and proliferated properly[74].

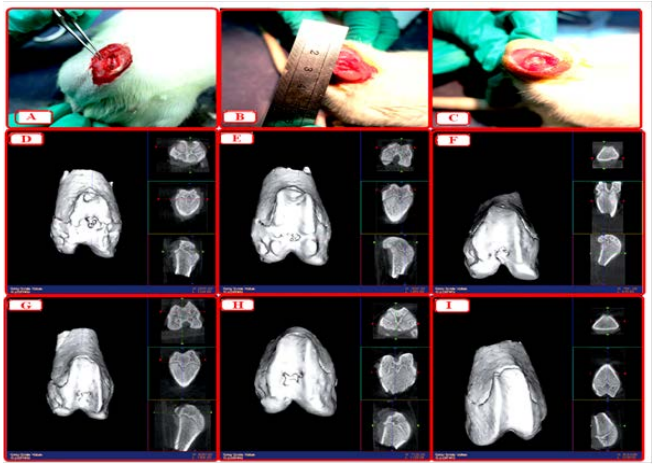

Figure 3. (A–C): Animal-tests and general observation of the knee-joints; (D-I): 3D reconstruction via micro-CT and iconography-observation of the knee-joints [7].

PLGA Nanostructure scaffolds were produced via freeze drying method with PLGA and Poly(N-Isopropylacrylamide) Nanoparticles and insulin like growth factor I, and transform growth factor ß1(Double growth-factor) bio-active agents for cartilage tissue engineering[46].

Yu et al. designed a bioactive resveratrol PLA-GEL Nano fibrous scaffold by means of electro-spinning, freeze drying, and uniform dispersion methods for repairing cartilage deficiencies. When the resveratrol PLA-GEL Nano fibrous scaffold was used, the repaired cartilage and sub-chondral bone were in improved condition (figure 4). The expression ranks of SIRT1, type II collagen, and PI3K/AKT signaling pathway-related proteins (AKT, VEGF, PTEN, Caspase 9, and MMP13) improved meaningfully. The expression levels of SIRT1,AKT and type II collagen proteins were augmented, whereas the expression levels of VEGF, PTEN, Caspase9 and MMP13 proteins were reduced ominously compared with the repair involved blank PLA-GEL Nano fibrous scaffold and without scaffold [100].

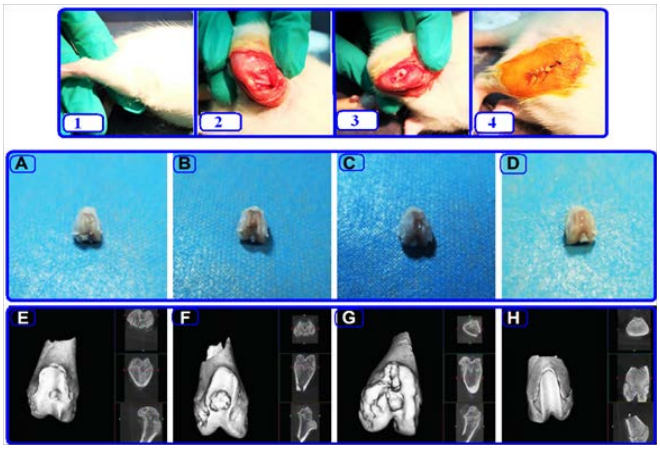

Figure 4. Treatment of the Sprague Dawley rats: (1) Select the surgical site, (2) Expose the surgical site, (3) Drill the hole and insert with or without nano-scaffold, (4) Close the surgical site; General observation and micro CT(Computed Tomography) observation of the knee joints : [A-D] General observation. [E–H] Micro observation, [A and E] The bio-active resveratrol PLA-Gel nano-fibrous scaffold, [B and F) The blank porous PLA-Gel nano-fibrous scaffold, [C and G] No scaffold , [D and H] The sham group [100].

In a different work, 3Dimention scaffold of PLA-GEL Nano fibers has been constructed for cartilage regeneration. To further improve the repairing effect of cartilage, a modified scaffold cross-linked with Hyaluronic Acid was also successfully fabricated. The consequences specified that the PLA scaffolds presented super absorbent specifications and exceptional cytocompatibility. PLA scaffolds showed elastic property in the wet condition and *in vivo* assay displayed that PLA-GEL scaffold cross linked with Hyaluronic Acid , might help the cartilage-regeneration figure 5 [53].

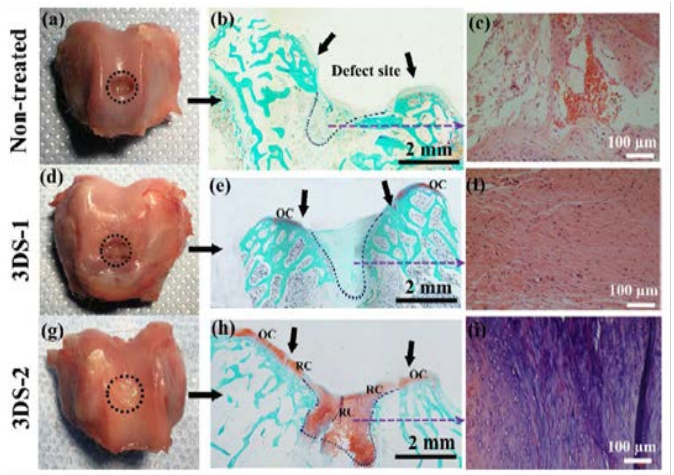

Figure 5. Macroscopic images (a, d, and g) of the cartilage joints from three groupsat 12 weeks after surgery. Histological-analysis of cartilage defect area from threegroups at 12 weeks after surgery, stained with Safranin O-fast green (b, e, and h) andH&E (c, f, and i). Arrows and dotted lines indicated the defect sites. OC: originalcartilage tissue, RC: repaired cartilage tissue [47].

In a different work, PLLA Nano fibrous scaffolds manufactured for delivering rat-MSCs in ligament-repairing, which resulted in enhancing mechanical strength and ligament regeneration[54].

Markowski et al. manufactured similar PLA composition for cartilage tissue engineering scaffolds. The hybrid structure of PLA and GEL Nano fibers, CNTs modified PLA Nano fibers, and pure PLA-based Nano fibers was produced in the form of fibrous membranes by electro spinning method. The scaffolds were investigated in cell culture of human chondrocytes collected from patients. To evaluate the effect of the Nano fibrous scaffolds upon chondrocytes, examinations for cytotoxicity and genotoxicity were carried out. The Nano fibrous structures were neither genotoxic nor cytotoxic, and their microstructure, physical and mechanical features produced suitable scaffolds for prospective utilization in cartilage repair[40].

Shi et al.[101], fabricated PLLGA scaffolds via carding and needle punch method for creating a Nano structure non-woven fibrous mat with PLGA Nanoparticles and BMP4 plasmid as bioactive agent. PLLGA scaffold was applied and bone morphogenetic protein 4 gene was delivered to adipose-derived stem cells for repairing articular cartilage.

In an exploration by *Haaparanta et al.*[15] PLA scaffolds were advanced for repairing the cartilage. PLA-Col, PLA-Chitason and PLA-Col-Chitason scaffolds were made-up via combining freeze dried natural components and synthetic PLA mesh. All the scaffolds displayed an extremely porous construction with open pores in the scaffold. The results showed that the PLA-Col scaffolds are the most hopeful scaffolds for cartilage tissue repair.

Ma et al.[102] used Paraffin spheres as porogens to construct PLLA scaffolds for cartilage regeneration. The scaffolds presented high cytocompatibility. Silk fibroin (SF) is another biomaterial extensively utilized for tissue regeneration since it displays nice biocompatibility, outstanding breathability, and biodegradability. The surface morphology, tensile strength, and degradation characteristics of the electro spun fibrous PLLA-SF scaffolds were examined for cartilage tissue engineering.

Liu et al. [17] constructed scaffolds via different electro spinning states, include collection distance, functioning voltage, and the SF:PLLA mass ratio. Besides, *in vitro* cell-scaffold interactions were estimated from the point of chondrocyte adhesion to the scaffolds in addition to the cytotoxicity and cytocompatibility of the samples. The best electro spinning states for producing a fibrous PLLA-SF scaffold with the finest surface morphology (arranged alignment and appropriate diameter) and tensile strength (~1.5 MPa) were a collection distance of 20 cm, a working voltage of 15 kV, and a PLLA-SF mass ratio of S50P50. The degradation rate of the PLLA-SF scaffolds was starting to be verified by the PLLA-SF mass ratio, and it can be enhanced by decreasing the PLLA percentage. Also, chondrocytes spread well on the fibrous PLLA-SF scaffolds and produced extracellular matrix, indicating nice adhesion to the scaffold. The cytotoxicity of PLLA-SF scaffold extract to chondrocytes over 24 and 48 hours in culture was low, showing that the PLLA-SF scaffolds are bio-compatible. Chondrocytes cultivated fine on the PLLA-SF scaffold after 1,3,5, and 7 days of direct contact, specifying the excellent cytocompatibility of the scaffold. The outcomes exhibit that the fibrous PLLA-SF scaffold characterizes a hopeful composite material for utilization in cartilage tissue engineering [17].

In another effort in 2017, PLLA Nano fibrous scaffold fabricated for delivering rat MSCs for ligament repair led to improved mechanical strength and tissue regeneration[54]. *Li et al.*[103], progressed Chondrocyte seeding-method and generated Homogeneous(Composed of parts or elements that are all of the same kind) PLLA Cell Nano fibrous mat. In a work by means of *Chen et al.* [14] in 2011, the surface of electro spun PLLA Nano fibers was treated with oxygen-plasma for introducing –COOH groups on the surface, followed by covalent grafting of CG-molecules onto the fiber surface, utilizing water soluble carbodiimide as a coupling agent[14,24]. Grafting cationized GEL (CG) with enhanced positive charge onto Nano fibers would be expected to support interaction of the positively charged fiber surface with the negatively charged cell membrane. CG was successfully anchored on the PLLA Nano fibers to develop their compatibility with chondrocytes, and to display *in vitro* and *in vivo* potential applications of CG grafted PLLA Nano fibrous membranes as a cartilage tissue engineering scaffold. Chondrocytes seeded in varied Nano fibers exhibited considerably different morphologies. Flat sheets of well-spread, fibroblast-like cells were found to be heavily attached to PLLA Nano fibers, pointing dedifferentiation of chondrocytes transpired on PLLA Nano fibers. Alternatively, globular, chondrocyte-like cells tightly attached to the Nano fibers and surrounded by a bulky ECM layer were obvious in PLLA-CG Nano fibers. These observations suggest that chondrocytes in the PLLA-CG Nano fibers are inclined to better keep their chondrocytes morphology than chondrocytes in the PLLA Nano fibers. Chondrocytes adapt well and spread not just on the surface of the NFM meshes, nonetheless as well in the interior area of the mesh structure. This chondrocyte can enter the PLLA-CG Nano fibers structure and utilize it to maintain for cell proliferation. Totally, *in vitro* studies indicated that chondrocytic activities for example cell proliferation; extracellular matrix fabrication and mRNA expression of cartilage ECM genes were increased in PLLA-CG Nano fibers in comparison to PLLA Nano fibers. *In vivo* evaluation of cartilage formation was approved after implantation of scaffolds in the back of 12-week-old New Zealand white rabbits (2.5 kg). Chondrocyte-seeded PLLA-CG Nano fibers were placed in the pockets

created on the backbone and the skin. Four weeks post-implantation, no local inflammatory warnings were determined at the working places and the incisions were entirely hidden and the pockets had diminished in size. A considerable decrease in membrane size was observed because of polymer degradation whereas the cartilaginous construct grown *in vivo* was in appearance with a yellowish white shade figure 6 [14].

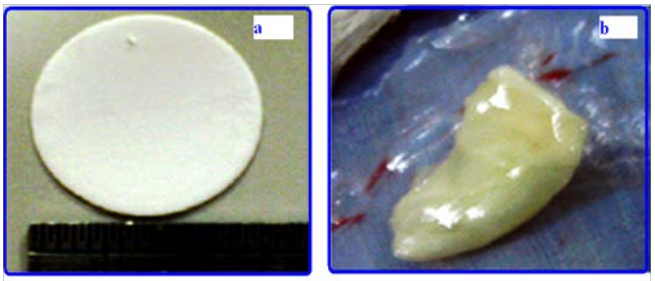

Figure 6. (a) PLLA-CG Nano fibrous scaffolds before implantation, (b) chondrocyte-scaffolds 4 weeks after grafting [14].

In vitro and *in vivo* tests displayed that chondrocytes seeded in PLLA-CG Nano fibers can grow into tissue like constructs with high viability, a round morphology and abundant deposition of sGAG (sulfated glycosaminoglycan) and type II collagen. These outcomes display the greater capability of PLLA Nano fibers after surface modification with CG to promote chondrocyte proliferation, differentiation and cartilaginous matrix biosynthesis[14].

Diao et al.[104], applied melt blending for fabricating PLA-Hydroxyapatite (HA) Nano composites. Surface modifying HA Nano particles (mHA) by means of dodecyl-alcohol via esterification-reaction might efficiently advance the dispensability of HA Nano particles in PLA-polymer and the interfacial interactions among PLA and HA Nanoparticles. PLA-mHA Nano composite established enhanced cartilage cell attachment, spreading and proliferation than that of PLA and PLA-HA film. The respectable cytocompatibility could be due to the good dispensability of the osteoinductive HA Nanoparticles, good interfacial interactions between PLA and HA Nanoparticles, and balanced hydrophobic-hydrophilic specification. In a different exploration, researchers constructed PLLA Nano-composite scaffold for repairing osteochondral-damage in a rabbit-model[105].

Ertan et al.[46] constructed poly(lactic acid-co-glycolic acid) Nano-scaffolds by means of freeze-drying method with Poly(Lactic Acid-co-Glycolic Acid) polymer and Poly(N-Isopropyl acrylamide) Nano-particles including Double Growth Factors IGF-I (Insulin-like Growth Factor I) and *TG-β1*(Transform Growth Factor β1) as bio-active agents.

A semi-crystalline di-block co-polymer, Poly(ε-caprolactone)-block Poly(L-lactide) (PCL-b-PLLA), was manufactured and used for fabricating Nano-fibrous scaffolds through a thermally-induced phase-separation method. Nano-fibrous construction and inter-connected porous configurations holding great pores were formed for *in-vitro* culturing of chondrocytes. Chondrocytes cultivated on the Nano-fibrous scaffold displayed a sphere-shaped chondrocyte like phenotype and concealed more cartilage like ECM than those cultivated on the solid walled scaffolds[106].

In an investigation by *Ito et al.*[105] a Nano scaffold was fabricated with including an atelo-collagen sponge and a PLLA mesh for repair of osteochondral damage in a rabbit model.

Saini et al. [107] stated that PLA Nano-scaffolds held chondrocyte proliferation and differentiation. Certainly, bovine chondrocytes cultured for 22 days on PLA Nano scaffolds in a concentric cylinder bioreactor under low oxygen tension improved the ECM production leading to concepts wherein an unformed cartilage like tissue was existing [107].

Table 3 sums up the chondrocyte activity and viability on different Nano fibrous PLA scaffolds, also Table 4 summarizes the characteristics of PLA Nanostructures in cartilage and joint regeneration.

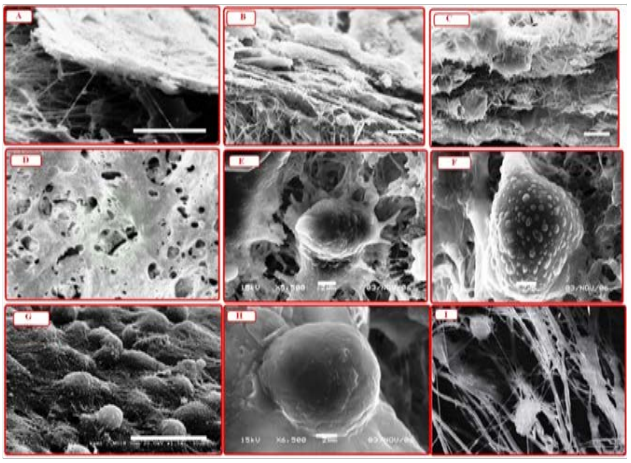

Figure 7. (A) PLA Nano-fibrous mat after 3 days Chondrocyte cultivation, (B) PLA CNT Nano-fibrous mat after 3 days Chondrocyte cultivation, (C) PLA-GEL Nano-fibrous mat after 3 days Chondrocyte cultivation, (D) PLGA Hyaluronic Acid Fibrin Bioactive Glass Nano-structure mat after 3 days Chondrocyte cultivation, E) PLLA-b-PCL Nano-fibrous mat after 12 hours Chondrocyte cultivation, F) PLLA b PCL Nano-fibrous mat after 1 day Chondrocyte cultivation, G)PLLA-b-PCL Nano-fibrous after 6 days Chondrocyte cultivation, (H) PLLA-b-PCL Nano-fibrous mat with solid-wall after 12 hours Chondrocyte cultivation, (I) PLLA SilkFibroin Nano-fibrous after Chondrocyte-cultivation [40,16].

Figure 7 illustrates the Chondrocyte cell morphology cultured on different PLA Nano fibrous scaffolds.

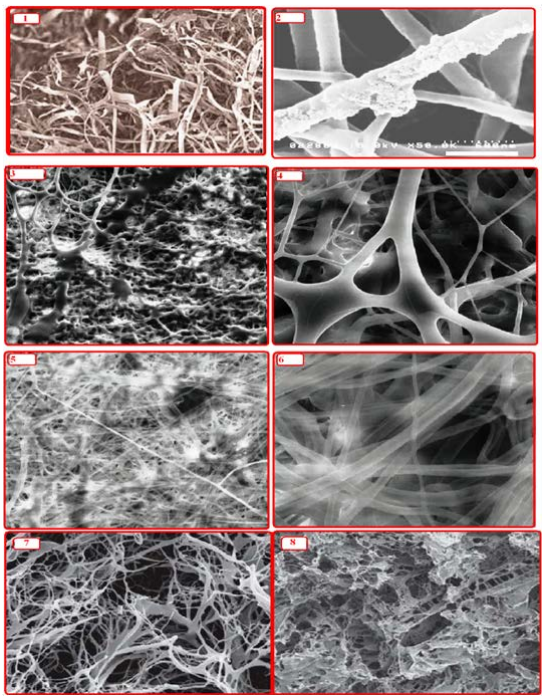

Figure 8. PLA Nano fibrous scaffolds for cartilage treatment: 1) PLA Gelatin Nanostructure scaffold, 2) PLLA-Cationized Gelatin Nano-fibers, 3) PLA-GEL Nano-fibrous scaffold, 4) PLA-GEL Nanofibrous scaffold, 5) PLA CNTNano-fibrous scaffold, 6) PLA CNTNano-fibrous scaffold, 7) PCL-b-PLLA Nanostructure scaffolds, 8) PCL-bPLLA Nano-structure scaffolds with macro-porous construction [14,40,106].

Type of scaffold	Type of Cells	Contents of Protein of the Cells (µg)			Contents of DNA of the Cells(µg)			Unit of cell viability	Cell viability						Unit of Proliferation	Proliferation of ECM production by chondrocytes (According to number of the days)							Cytotoxicity	Ref.*
		3	6	12	3	6	12		1	2	3	5	7	14		1	2	3	7	14	21	28		
PLLA-Silk Fibroin	Chondrocyte	-	-	-	-	-	-	Absorbance at 490 nm	0.24	-	0.42	0.73	0.9	-	Optical Density	0.529 ±0.004	0.809 ±0.013	-	-	-	-	-	-	[17]
PLLA	Chondrocyte	-	-	-	-	-	-	Absorbance at 490 nm	0.22	-	0.31	0.57	0.7	-	Optical Density	-	-	-	-	-	-	-	-	
PCL-b-PLLA Nano-fibrous scaffold	Chondrocyte	50	82	120	3	5	7	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-	[106]
PCL-b-PLLA SW scaffold	Chondrocyte	38	60	90	2.5	3.8	5.8	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-	
PLA	Chondrocyte	-		-	-	-	-	(%) [Alamar Blue Assay]	-	96	-		-	-	-	-	-	-	-	-	-	-	87% of control	[40]
PLA/GEL	Chondrocyte	-		-	-	-	-	(%)[Alamar Blue Assay]	-	82	-		-	-	-	-	-	-	-	-	-	-		
PLA / CNT	Chondrocyte	-		-	-	-	-	(%)[Alamar Blue Assay]	-	100	-		-	-	-	-	-	-	-	-	-	-	50% of control	
PLLA	Chondrocyte	-		-	-	-	-	Absorbance at 490 nm [MTS Assay]	1.5	1.7	2.2		3	3.7	cell number ×104	-	-	13	18	23	28	29	-	[14]
PLLA- CG	Chondrocyte	-		-	-	-	-	Absorbance at 490 nm [MTS Assay]	2	2.2	2.6		3.6	4.4	cell number ×104	-	-	16	24	30	32	35	-	
PLGA	hADMSCs	-		-	-	-	-	O.D. [MTT Assay]	0.4	0.4	0.75		-	-	-	-	-	-	-	-	-	-	-	[74]
PLGA + 50% Ha + 25% Fibrin + 25% Bio-active Glass	hADMSCs	-		-	-	-	-	O.D. [MTT Assay]	0.8	0.8	1.2		-	-	-	-	-	-	-	-	-	-	-	
PLGA + 25% Ha + 50% Fibrin + 25% Bio-active Glass	hADMSCs	-		-	-	-	-	O.D. [MTT Assay]	1.75	7.15	2.25		-	-	-	-	-	-	-	-	-	-	-	
PLGA + 10% Ha + 80% Fibrin + 10% Bio-active Glass	hADMSCs	-		-	-	-	-	O.D. [MTT Assay]	0.95	0.95	1.5		-	-	-	-	-	-	-	-	-	-	-	

Table 3. Chondrocyte activity and viability on PLA Nano fibrous scaffolds.

*Ref: Reference number

PLA Nano-structure	Fiber Diameter (nm)	Porosity	Water Absorbtion (%)		Contact Angle (Degree)	Pore Size (µm)	Electrical Resistivity (Ωm)	Crystallinity (%)	Specific Surface (m /g)	Weight Loss (%) (After soaking in PBS solution)						Compression Modulus (kPa)	Tensile strength (MPa)	Breaking Strain (%)	Ref.
			1 Day	28 Day						1 Day	14 Day	28 Day	42 Days	56 Days	84 Days				
PLLA: Silk Fibroin 50:50	750	-	-	-	-	-	-	-	-	20	27	45	53	63	92	-	0.2	1.8	[17]
PLLA: Silk Fibroin 40:60	990	-	-	-	-	-	-	-	-	18	25	35	47	55	65	-	1.55	3	
PLLA: Silk Fibroin 60:40	950	-	-	-	-	-	-	-	-	17	23	35	43	47	55	-	1.2	1.8	
PLLA	220	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PLA	2890	83	-	-	108.5 ± 1.4	-	>1015	45	-	-	-	-	-	-	-	178 ± 14	1.8 ± 0.4	-	[40]
PLA-CNT	2080	80	-	-	95.4 ± 1.9	-	6.7	51	-	-	-	-	-	-	-	461 ± 39	8.8 ± 0.7	-	
PLA-GEL	1120(PLA)/ 2090(GEL)	73	-	-	84 ± 2.2	-	-	41	-	-	-	-	-	-	-	375 ± 22	6.2 ± 0.3	-	
PCL-b-PLLA Nano-fibrous scaffold	100-170	93.0% ± 1.0%	-	-	-	144±36	-	-	8.09±0.23	-	-	-	-	-	-	108±20	-	-	[106]
PCL-b-PLLA SW scaffold	-	95.5% ± 1.5%	-	-	-	168±69 / 40±15	-	-	2.90±0.45	-	-	-	-	-	-	90±15	-		
PLGA	-	-	400	580	-	-	-	-	-	2.5	6	9	-	-	-	-	-	-	[74]
PLGA + 50% Ha + 25% Fibrin + 25% Bio-active Glass	-	-	750	780	-	-	-	-	-	2.5	9	10.5	-	-	-	-	-	-	
PLGA + 25% Ha + 50% Fibrin + 25% Bio-active Glass	-	-	750	800	-	-	-	-	-	5.5	11.5	12	-	-	-	-	-	-	

PLGA + 10% Ha + 80% Fibrin + 10% Bio-active Glass	-	-	750	820	-	-	-	-	-	2.5	7.5	9.5	-	-	-	-	-	-

Table 4. Specifications of PLA Nano-structures used for cartilage repair.

The SEM photographs of different PLA Nano fibrous scaffolds for cartilage tissue engineering applications are shown in figure 8.

Conclusions

In summary, there is an immense potential for advancing present cartilage-therapies to attaining an unswervingly effective method used for cartilage diseases. Tissue Engineering might be the greatest technique for success of this method using capable cell-sources, for instance Stem-Cells, New Bio-logically Inspired Scaffolds or Scaffold-less Methods, Developing Nano-Technology, Chondro-Genic Factors, and Physical Stimuli. Nonetheless, there are a number of important questions about Cartilage Patho-physiology, still remained un-answered. Also, the controlling trails that impending cartilage-therapies seem need to follow are quiet un-folding. However, noteworthy suggestion occurs currently assistant the notion that tissue engineered cartilage re-presents a possibly forceful methodology to efficiently treat cartilage injury or trauma.

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