International Journal of Medical Laboratory 2021;8(1):1-9.

International Journal of Medical Laboratory
Shahid Sadoughi University of Medical Sciences

Review Article

A Review of Tissue-Engineered Cartilage Utilizing Fibrin and Its Composite

Majid Pourentezari[1] Ph.D., Morteza Anvari[1] Ph.D., Maryam Yadegari[1] Ph.D., Abolghasem Abbasi[1] Ph.D., Hengameh Dortaj[2*] Ph.D.

[1] Department of Anatomy and Molecular Biology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] Department of Tissue Engineering and Applied Cell Science, Shiraz University of Applied Medical Science and Technologies, Shiraz, Iran

Article history
Received: 21 Jul 2020
Accepted: 22 Nov 2020
Available online: 4 Mar 2021

Keywords
Fibrin
Fibrin composite
Fibrinogen
Cartilage
Scaffold

A B S T R A C T

Suitable alternatives are made for damaged or diseased organs and tissues in tissue engineering by combining cellular and molecular biology with materials and mechanical engineering. Fibrin is a critical blood component responsible for homeostasis, used extensively as a biopolymer scaffold in tissue engineering. This study summarizes the latest developments in organ and tissue regeneration using fibrin as a scaffold material. The combination of active peptides and growth factors through a heparin-bound delivery system improves fibrin function as a scaffold. Besides, the development of fibrin precursors as recombinant proteins solves multiple or single donor fibrin adhesives. Its composite allows biomolecules to be combined with fibrin and can significantly enhance fibrin efficacy in cartilage tissue engineering applications.

[*]**Corresponding Author:** Department of Tissue Engineering and Applied Cell Science, Shiraz University of Applied Medical Science and Technologies, Shiraz, Iran. **Tel:** +983538203410, **Email:** hengameh.dourtaj@gmail.com

[DOI: 10.18502/ijml.v8i1.5665]

Introduction

Loss or destruction of tissues and organs due to aging or pathological conditions is crucial in human health. Although the body itself can usually repair most injuries at an early age, some parts of the body have limited repair capacity. Cartilage has a limited ability to repair the damage because it has no blood vessels and nerves [1, 2]. The limited self-healing capacity of cartilage has encouraged researchers to develop new and biometric technologies to improve tissue integrity. Recently, tissue engineering has emerged as a new method of treating damaged or disabled tissue such as cartilage, bone, and skin [3]. Creating an optimal tissue engineering structure requires three basic components: a suitable cell source, growth and differentiation factors, and a suitable scaffold to support cell regeneration based on cell type.

To design scaffold for cartilage repair, materials should be used that have biochemical and physical properties for better engineering of cartilage tissue structures. Biochemical design is related to the chemical composition and biological properties of scaffolding, affecting cell behavior and activity. The physical design is associated with the scaffold's interior and exterior architecture, mechanical properties, and destruction. Designing an ideal scaffold with a proper physical structure, the possibility of adhesion, migration, and differentiation of cells is important. Scaffolds can be made of natural, synthetic, or hybrid materials [4, 5].

Natural materials often have physiological activities such as cell adhesion, adaptability, and proper degradation. There are two kinds of naturally derived polymers. Carbohydrate-based polymers such as agarose, alginate, hyaluronic acid, and protein matrices such as fibrin and collagen are in this category [6].

Composition, structure, and properties of fibrin

Fibrin is a natural biodegradable material used as an efficient scaffold engineering of many tissues. A fibrin scaffold is a protein network formed by the polymerization of fibrin monomers and protects a variety of living tissues. Fibrin is a biomaterial that naturally consists of a network with transverse connections that has led to its widespread use in medical applications. Fibrin has a high potential for use in tissue engineering. It can be isolated from the patient's blood and used as a potentially safe autologous scaffold for a foreign body interaction or infection [7-9]. Fibrin acts as an active matrix due to its numerous interaction sites for cells and other proteins and is suitable for cell delivery systems and biomedical drugs and molecules [10].

Fibrin is proinflammatory and induces its degradation and substitution by cellular components of the extravascular tissue spaces, and its degradation products are nontoxic physiological substances. Fibrin has been extensively used as scaffold material by incorporating chondrocytes into the fibrin clot, both *in-vitro* [11] and *in-vivo* [12]. Peretti et al. reviewed the studies of fibrin hydrogels in articular cartilage repair in laboratory animals. They suggested that the mixture of autologous

[DOI: 10.18502/ijml.v8i1.5665]

chondrocytes and allogeneic decellularised cartilage matrices suspended in fibrin glue led to the generation of cartilage-resembling constructs [13].

Microfracture is the most common restorative method used to treat articular cartilage in the clinic. During the microfracture procedure, articular cartilage defects are created by small holes within the subchondral bone. These holes permit the constitution of the clot at the defect site. Progenitor cells and growth factors can incorporate into the defect site and inchoate the tissue's repair by creating a fibrocartilage-like tissue [14, 15]. One study found that using fibrin scaffolds to cultivate human mesenchyme stem cells under laboratory conditions and living organisms increased cell proliferation and survival [16]. The fibrin scaffold increases vertebral disc cells' proliferation compared to the alginate scaffold and reduces cell apoptosis [17]. Fibrin has been used successfully as a scaffold to repair fibrocartilage, elastic cartilage, cranial and facial cartilage, and articular cartilage. Collagen fibrin hydrogels permit the organization of an enduring bond in a cartilage repair chicken model [18]. Fibrin encapsulated chondrocytes in articular cartilage tissue engineering have been widely used in practical studies [19-21].

Biological properties of fibrin

Fibrin is a biopolymer of fibrinogen monomers. The fibrinogen molecule is composed of two sets of three polypeptide chains called Aa, B, and y, joined together by six disulfide bonds [22]. Fibrin mediates blood platelets' formation and the expansion of endothelial cells, the proliferation of fibroblasts in the tissue, and the angiogenic process's strengthening, thereby accelerating the wound healing process [23]. Fibrin prevents further blood loss and also provides a temporary scaffold to support tissue repair and regeneration [24].

Although standard quality fibrin glue is produced, autologous fibrin glue has two significant advantages: the reduced possibility of viral transmission and infection and the lower cost [25, 26]. Fibrin glue for tissue engineering serves as a delivery carrier and as a scaffolding matrix [27]. Fibrin glue can be modified in mechanical properties by applying other polymers such as gelatin, hyaluronic acid, and chondroitin sulfate [21].

Mechanical properties of fibrin

The configuration of the scaffold is serious about supporting cartilage regeneration. With the improvement in the manufacture and shape of the scaffold, a three-dimensional (3D) structure is precedent to two-dimensional (2D) due to further maintenance of cell structure, differentiation, and resemblance of morphology and growth of cells [28]. Fibrin stiffness behavior is subordinated by the phenomenon called "strain hardening": at low pressures, the stress is directly proportional to the pressure. However, in large strains, the fibrin stiffness increases with rising pressure up to 20-fold [29]. However, fibrin scaffolds have poor mechanical properties and fast degradation, limiting the time needed for the formation of neocartilage [30, 31]. The mechanical reactions of fibrin gels to shear, tensile, and compressive forces are known to represent a completely nonlinear reaction known as strain

[DOI: 10.18502/ijml.v8i1.5665]

hardening [32]. The composition of polylactic acid with glycolic acid with fibrin increases the elastic modulus of scaffolding, while it has no side effects on cell proliferation and secretion of glycosaminoglycan [33]. By culturing stem cells in a fibrin scaffold as a three-dimensional scaffold, researchers stated that cell survival and proliferation increased and could induce osteogenic, chondrogenic, and adipogenic dynasties [34]. Natural scaffolds such as fibrin could be a proper environment for differentiating mesenchyme stem cells in the presence of transforming growth factor beta (TGF-β) [1]. In cartilage defect treatment, scaffolds are often fixed with fibrin glue to stay in place to inject and localize cells in the defect sites. Fibrin hydrogels could be an attractive carrier for mesenchymal stroma cells (MSC)-based tissue engineering approaches [35]. Fibrin hydrogels permit the high efficiency of cell seeding, better adhesion of cells, and uniform distribution [36]. This study reviewed and summarized the specifications of fibrin scaffold and composite/hybrid scaffolds based on fibrin, along with growth factors and cells in cartilage tissue engineering (Tables 1, 2).

Table 1. Overview of investigated fibrin scaffolds in cartilage tissue engineering

Author	Year	Scaffold type	Growth factor	Method of study	outcome
Liu Y [36]	2009	Fibrin	Collagenase-treated medium	*In-vitro*/ human septal cartilage chips chondrocytes	Fibrin preparations increased cellular proliferation and DNA content. increased GAG accumulation
Haleem AM [37]	2010	PRF	CM	*In-vivo*/ human BMSCs	Transplanting autologous BM-MSC in PR-FG as a cell scaffold is an effective procedure for better repairing articular cartilage defects in human patients.
Jung SN [38]	2010	Fibrin	CM	*In-vivo*/ hADSCs in subcutaneously in nude mouse	Increased expression of aggrecan cartilage genes, type II collagen, and SOX-9 was observed and showed that mesenchymal stem cells of cartilage differentiation from human adipose tissue with fibrin adhesive could proliferate and subcutaneously form new cartilage in the back of nude mice
Park JS [39]	2011	Fibrin	CM+ TGF-β3	*In-vitro*/ human BMSCs-amniotic fluid *In-vivo*/ nude mice	The results of both in vitro and in vivo studies showed that cultured or transplanted hMSC cells are mixed with TGF-β3 in fibrin hydrogel differentiate into chondrocytes.
Ahmed TA [40]	2011	Fibrin	CM+ TGF-β2	*In-vitro*/ human BMSCs	BMSCs in FG demonstrated an increase in Aggrecan gene expression and accumulation of ECM.
Deponti D [41]	2012	Fibrin	CM	*In-vitro- In-vivo*/ swine chondrocytes	The *In-vivo* culture showed further tissue maturation compared to in the *In-vitro* condition.
Dai Y [42]	2016	Fibrin	CM	*In-vivo*/ Rabbit BMSCs	Cartilage-related genes and proteins were up-regulated, and deposition of collagen type II and GAGs in the neo-cartilage demonstrated.
Souza FG [43]	2017	PRF	CM	*In-vitro*/ hADSCs	More proliferation and differentiation into cartilage was demonstrated in mucopolysaccharide in the matrix of cells marked with the toluidine blue.
Izadi MA [44]	2017	Fibrin	CM+ Kartogenin / CM+ TGF-β3	*In-vitro*/ hADSCs	Expression of the chondrogenesis gene marker, SOX9, Aggrecan, and type II collagen, was observed in the Kartogenin and TGFβ3 groups compared with the control group. The expression of type X collagen as a marker of hypertrophy in ketogenic exposed cartilage was also decreased.

[DOI: 10.18502/ijml.v8i1.5665]

Izadi MA [45]	2018	Fibrin	CM+ Kartogenin/ CM+ Avocado soybean	*In-vitro*/ hADSCs	ASU in fibrin scaffold raised the expression of COL II and AGG.
Iseki T [46]	2019	Fibrin	CM	*In-vitro*/ BMSCs	Applying dynamic compressive force enhanced chondrogenesis and maturation in a simulated *In-vitro* model of fracture.
Ghiasi M [47]	2019	Fibrin	CM+TGF-β	*In-vitro*/ hADSCs	Fibrin scaffold had a high expression in chondrogenic gens. A new strategy for tissue regeneration utilization of inherent scaffolds such as fibrin can act as a protector for MSCs.
Wong CC [48]	2020	PRF	CM	*In-vitro*/ porcine chondrocytes	PRF promotes the survival and expression of GAG. PRF conditioning media persuade notable migration and growth of cartilage cells from grafts.
Kim JS [49]	2020	Fibrin	CM	*In-vitro*/ hADSCs	Extension of the concentrations of fibrinogen and thrombin caused stiffness. Besides, hADSCs within high-concentration fibrinogen formulation maintained a morphology near to natural chondrocytes.

hBMSCs= Human bone marrow stem cells; CM= Chondrogenic medium; PRF= Platelet-rich fibrin; ECM= Extracellular matrix; hADSC= Human adipose-derived stem cells; TGF-β= Growth factor beta

Conclusions

Despite the availability of a wide range of surgical procedures to treat cartilage lesions, which have been successful in the short and sometimes long term, none of these procedures are yet able to restore the function and structure of damaged cartilage fully. Cartilage tissue engineering requires a suitable microenvironment that can act as an extra-cellular matrix in which cells proliferate and differentiate. Fibrin is one of the most promising polymers used in cartilage tissue engineering applications, and the administration of fibrin in this field is still developing. Commercial fibrin adhesives are expensive and are also associated with disease transmission. Also, these products are diverse from batch to batch. The combination of immaterial and fibrin has demonstrated the great possibility of maximizing its interactions with cells due to the enhancement in surface area and its capability to handle its biological activity. Further research is required to optimize the prosperous condition of fibrin-based strategies for restoring damaged articular cartilage to enhance fibrin-based engineered structures' mechanical properties and understand the cellular signaling involved in cartilage formation better.

Table 2. Overview of investigated fibrin composite/hybrid scaffolds in cartilage tissue engineering

Author	Year	Scaffolds Type	Growth Factor	Cells/ Model	Outcome
Rampichová M [50]	2010	Fibrin/ hyaluronic acid	CM	*In-vivo*/Pig chondrocytes	Regenerated cartilage showed good biomechanical and histological properties six months after implantation. The repair quality process depended on the initial chondrocyte concentration seeded.
Zheng Q [51]	2010	PLGA/fibrin	CM	*In-vitro*/ Rat BMSCs	Reinforcing the fibrin scaffolds and maintaining their interspace improved cell proliferation.
Wang W [52]	2011	PLGA/fibrin	CM	*In-vitro*/ Rabbit chondrocytes	Maintain phenotype, and increase the GAG secretion

[DOI: 10.18502/ijml.v8i1.5665]

Park SH [53]	2012	Alginate coating in HA/fibrin composite	CM	*In-vivo*/ Rabbit chondrocytes in subcutaneous of nude mice	The chondrogenic differentiation was showed in alginate coated fibrin/HA composite gel without a size reduction. The coating provided a suitable environment for cartilage without using any growth factors.
Li B [54]	2013	PLGA/fibrin	CM+poly (ethylene oxide)-b-poly(L-lysine)/ TGF-b1 plasmid DNA complexes	*In-vivo*/ Rabbit BMSCs	Increasing the cartilage specific genes, and increasing the GAG secretion
Kreuz PC [55]	2013	Fibrin/ polyglycolic acid (PGA)	CM	*In-vivo*/ Human chondrocytes In subcutaneous nude mice	Constitution of type II collagen rich hyaline cartilage
Hong HJ [56]	2014	PLGA/fibrin/ hyaluronan	CM	*In-vivo*/ Rabbit Chondrocytes	Tracheal reconstruction, favorable mechanical and functional recovery
Wang ZH [57]	2016	Fibrin/bone matrix gelatin (BMG)	CM	*In-vitro*/ Rat Chondrocytes	Cells on the BMG/fibrin glue scaffold showed a round morphology, while the chitosan/gelatin group had a spindle-like shape. Chitosan/gelatin scaffolds had BMG/fibrin glue constructs that supported chondrocyte proliferation, attachment, and ECM synthesis.
Gupta N [58]	2019	Fibrin-Genipin	CM	*In-vitro*/ Rabbit chondrocytes	Genipin cross-linked fibrin hydrogels modified fibrin's mechanical properties by increasing the tensile, compression, and shear stress.
Hashemibeni B [59]	2019	PLGA/Fibrin	CM+Avocado/ Soybean MC+ TGF-β3	*In-vitro*/ hADSCs	ASU can induce chondrogenesis in hADSCs in PLGA/ fibrin scaffold. Increase of special markers of hyaline cartilage and reduce hypertrophic and fibrosis markers compared to the growth factor TGF-β3.
Gorji M [9]	2020	PLGA/Fibrin nanoparticles	CM+icariin+ TGF-β3	*In-vitro*/ hADSCs	Increasing the cartilaginous-specific gene expression, decreasing the Coll I gene expression, and the differentiation of hADSCs to chondrocytes
Monaco G [60]	2020	Fibrin/ polyurethane	TGFβ1/hMwt HA	*In-vitro*/ Human BMSCs	HA increased the synthesis of GAGs, especially in the early days of chondrogenesis, and reduced the Coll X gene expression's up-regulation. hMwt HA added inside the fibrin led to better ECM construction.

hBMSCs= Human bone marrow stem cells; CM= Chondrogenic medium; PRF= Platelet-rich fibrin; ECM= Extracellular matrix; hADSC= Human adipose-derived stem cells; TGF-β= Growth factor beta; hMwt HA= High molecular weight hyaluronan; PLGA= poly (l-lactic-co- glycolic acid

Conflict of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Acknowledgment

The authors thank all the contributors of the Department of Anatomy and Molecular Biology, University of Medical Sciences, Yazd, Iran.

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[DOI: 10.18502/ijml.v8i1.5665]

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[DOI: 10.18502/ijml.v8i1.5665]