



Recent Developments in Cell-Loaded Collagen Scaffolds and Their Biomedical Applications

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ABSTRACT

By using the extracellular matrix for tissue healing, tissue engineering approaches aim to improve or replace organic tissues and organs. The biocompatibility, low immunogenicity, biodegradability, hemostatic qualities, and mechanical strength of collagen-based scaffolds are highlighted because they promote cell adhesion, migration, proliferation, and differentiation. In addition to examining the creation of cell-loaded collagen scaffolds and their uses in skin, nerve, bone/cartilage, heart, and liver tissues, the review delves into the composition, structure, biological characteristics, and crucial role that collagen plays in cellular interactions. Additionally, new approaches and prospects for therapeutic tissue restoration are described, highlighting the promise of collagen scaffolds as cutting-edge biomaterials in growing clinical applications.

Keywords: Collagen scaffolds, Cell loaded, Tissue Engineering, Regenerative medicine

INTRODUCTION

Tissue and organ regeneration after injury is a complex challenge due to human tissues' limited regenerative capacity, particularly under pathological conditions. Recent developments in tissue engineering have suggested using scaffolds that resemble the extracellular matrix to solve tissue dysfunctions and organ shortages. By supplying vital nutrients and providing appropriate characteristics for tissue repair, these scaffolds promote healing. Three essential elements are needed for a successful tissue-engineered scaffold: growth factors, scaffold biomaterials, and an appropriate cell supply. ^[1,2]

Natural polymers, like collagen and gelatin, and synthetic polymers, such polyethylene glycol, are the two categories of materials used in tissue engineering. Because of its low immunogenicity, biocompatibility, and degradability, collagen—which comes from the extracellular matrix—helps with tissue healing and cell adhesion. Although gelatin, a collagen derivative, retains biological capabilities and has better water solubility, it does not completely mimic the triple-helix structure of collagen. Collagen is a useful scaffold in regenerative medicine applications because it can act as a carrier for medication delivery and contributes to hemostasis by activating coagulation factors, which stops bleeding. ^[3,4]

The structure, biological characteristics, and function of collagen in controlling cellular behavior are highlighted in this article. The preparation of collagen scaffolds and their particular uses in tissues such as skin, nerves, bone, heart, and liver are described, and the article concludes with future directions for collagen research.

COLLAGEN SOURCES, STRUCTURE AND PROPERTIES

Forty vertebrate collagen genes have been found so far, resulting in 29 distinct homo- or heterotrimers. Type I collagens are usually heterotrimers consisting of two $\alpha 1$ chains and one $\alpha 2$ chain, whereas types II, III, and VII are homotrimers. While type II collagen is derived from the cartilage of cows, pigs, and chickens, type I collagen is mostly collected from the skin and tendon tissues of mammals. Furthermore, marine species like fish and jellyfish, as well as sustainable byproducts like fish bones and skin, can be



used to make collagen. Collagen, which is present in the skin, intervertebral discs, tendons, bones, cornea, and placenta, accounts for almost 30% of all protein in humans. ^[5,6]

The repeating amino acid sequence [Gly-X-Y]_n, which forms an α -helix with proline and hydroxyproline in the X and Y locations, is what defines collagen's fundamental structure. Tropocollagen, its tertiary structure, is made up of three left-handed helical polypeptide chains stacked in a superhelix and is around 300 nm long and 1.5 nm in diameter. Tropocollagen is used to create collagen microfibers, which have a D-type cycle band gap of roughly 67 nm, a staggered quarter-cycle configuration, and are cross-linked by covalent connections. Collagen's triple helix structure and protofibrils, which are maintained via intrachain $n \rightarrow \pi^*$ interactions and interchain hydrogen bonds, are what give it its mechanical strength. Through variations in helix spacing, kinetics, and thermal stability, variations in the Gly-X-Y sequence affect the mechanical characteristics of collagen. Protofibrils are joined by hydrogen bonds and other interactions, whereas collagen chains are joined by covalent connections. The size and configuration of collagen fibers influence the mechanical characteristics of tissue. ^[7]

Collagen is broken down by special enzymes found in living things called matrix metalloproteinases (MMPs). By harming basement membrane proteins and impairing keratinocyte migration and epidermal repair, overexpression of MMP-9 in chronic wounds impedes healing. Collagen has the ability to attach to MMPs, preventing them from acting and shielding the extracellular matrix. Moreover, MMP activity and inflammation are decreased by increasing the expression of tissue inhibitor of metalloproteinase (TIMP). ^[8]

EFFECTS OF COLLAGEN ON CELLULAR BEHAVIOR

Collagens control migration, growth, and differentiation via interacting with cells via receptors. Collagen binding to integrins and discoidin domain receptors (DDR) is necessary for cell adhesion; G α OGE α binds to integrins $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$, and $\alpha 11\beta 1$. DDRs, primarily DDR1 and DDR2, regulate cellular adhesion and migration by activating upon collagen binding. Through the MAPK/ERK pathway, DDR1, which is expressed in a variety of cells and interacts with collagen types I–IV, affects immune cell motility. By controlling matrix metalloproteinases (MMPs) and encouraging chemotactic migration through collagen degradation, DDR2 primarily binds to collagen types I and III, improving cell migration. Fibroblast migration in lung tissue requires MMP-2 and MMP-10. ^[9, 10]

Through processes like chemotaxis, haptotaxis, durotaxis, and contact guidance, cells migrate in response to environmental stimuli. Anisotropic alterations in the collagen matrix brought on by local collagen deposition or cell-mediated tension cause haptotaxis. Collagen matrix stiffness influences durotactic migration, resulting in movement along stiffness gradients. Furthermore, cells interact with the structure of collagen fibers to facilitate contact-guided migration, which accelerates and prolongs migration.

The extracellular environment has a major impact on cell proliferation, particularly during tissue healing following injury. The main extracellular matrix protein in the dermis, collagen, is essential for wound healing and tissue homeostasis. Collagen and matrix metalloproteinases (MMPs), especially MMP-2, which are produced by fibroblasts, are involved in the production and modification of the matrix during healing. DDR2 is essential for controlling the expression of collagen and MMP, which encourages the growth of fibroblasts. While MMP-2 aids in matrix disintegration and releases growth factors that further boost fibroblast activity, increased DDR2 promotes collagen synthesis. Mice lacking DDR2 have poor wound healing, as evidenced by decreased collagen and fibroblast activity. On the other hand, increased collagen deposition is correlated with dysregulated DDR1 expression in keloid fibroblasts. MMP-1 is released by activated platelets and collagen dressings, which promotes fibroblast migration and proliferation. Macrophages provide growth factors that promote angiogenesis and fibroplasia, promoting the proliferation of endothelial cells required for tissue healing. ^[11]

Stem cells, which include pluripotent, embryonic, mesenchymal, hematopoietic, and neural stem cells, are undifferentiated, self-replicating cells. Factors such as scaffold fiber diameter, pore shape, and matrix stiffness influence their differentiation. Collagen hydrogels, for example, can increase SOX-9 expression, which helps mesenchymal stem cells differentiate into chondrocytes through ROCK-dependent actinomyosin contraction. They also affect other cell types, including adult mouse myoblasts and human dermal fibroblasts. ^[12]

COLLAGEN SCAFFOLD PREPARATION

Chemical Cross-Linking

Chemically cross-linked hydrogels are generated by covalent bonding between polymer chains using a variety of processes, including Schiff base creation, Michael addition, condensation, 'click' chemistry, UV cross-linking, free-radical polymerization, and enzyme-induced cross-linking. They have better mechanical characteristics and stability than physically cross-linked hydrogels.



(i) Click Chemistry

"Click chemistry" is a combinatorial chemical technique that uses important processes like cycloaddition, nucleophilic ring-opening, and the chemistry of non-alcoholic aldehydes to create carbon-heteroatom (C-X-C) bonds. Thiol-alkene click chemistry is a prominent technique that produces sulfur radicals that enable Michael additions to olefinic double bonds by activating thiols with light or thermal initiators. Thiolate anions can attack activated olefins nucleophilically to create thioether linkages in alkaline environments. Click-functional groups in natural macromolecules are necessary for this effective reaction. Notable uses include the development of hydrogels with thiol-modified collagen and acrylate copolymers, which encourage the encapsulation and networking of stem cells, and the production of an injectable hydrogel using thiol-modified collagen and PEG-maleimide, which effectively maintained high cell viability. ^[13]

Strain-promoted azide-alkyne cycloaddition (SPAAC) is a copper-free click chemistry process in which azide attacks alkyne carbon atoms nucleophilically, forming a five-membered ring via a [3 + 2] cycloaddition. This reaction is advantageous because it prevents copper toxicity, enabling the creation of scaffolds in living cells and in-situ tissue cross-linking. In order to produce an interpenetrating polymer network hydrogel that maintained corneal epithelial cells with a 99% survival rate, Chen et al. showed that they could cross-link collagen utilizing SPAAC and hyaluronic acid through a Michael addition. Furthermore, SPAAC can be used to immobilize epidermal growth factor (EGF) onto collagen, which enhances cell adhesion and proliferation and permits the addition of particular functional groups for effective gelation. ^[14]

(ii) Enzyme Cross-Linking

Benefits of enzyme cross-linking include low byproduct generation, high specificity, yield, and moderate reaction conditions. Lysine oxidase (LOX), glutamine transaminase (MTG), and horseradish peroxidase (HRP) are important enzymes that target amino groups to alter the stability, elasticity, and bioactivity of collagen. Enzyme concentration can influence gel strength, facilitating effective gelation. Although its use in the synthesis of biomaterials is restricted by reaction rate limitations, LOX, which is dependent on copper ions, catalyzes the oxidative deamination of lysine residues to generate durable cross-links.

As shown by Ying et al., who produced a hydrogel containing cross-linked collagen and tyrosinated hyaluronic acid that promoted the growth of human microvascular endothelial cells and fibroblasts, HRP uses H₂O₂ to catalyze free radical couplings in proteins, enabling non-specific cross-linking. ^[15] By promoting acyl transfer events between glutamine and lysine residues, MTG is a useful enzyme for increasing the mechanical strength of collagen. For example, Tayabally et al. demonstrated that greater MTG concentrations enhanced collagen fiber production and fibroblast proliferation, whereas hydrogels made from collagen cross-linked with transglutaminase promoted an appropriate environment for three-dimensional development of human dental pulp stem cells. ^[16]

(iii) Photoactivated Cross-Linking

Photoactivated cross-linking enables the rapid synthesis of hydrogel networks in mild conditions, with adjustable physicochemical features such as pore size and elastic modulus via light exposure and photoinitiator concentration. Methacrylate groups are incorporated into natural macromolecules to form photosensitive cross-linking sites. UV irradiation of photoinitiators produces free radicals, which induce chain polymerization and covalent cross-linking. He et al. produced light-cured collagen methacrylate (COLMA) and chondroitin methacrylate (CSMA), yielding a two-component CSMA-COLMA hydrogel matrix with high storage and elastic modulus. This hydrogel protects encapsulated keratinocytes and fibroblasts, improving cellular function and boosting chondrogenic activity. ^[17]

Riboflavin (RF), often known as vitamin B₂, is a crosslinking agent and photoinitiator in UV curing. Upon UV light absorption, RF transitions to an excited singlet state and then intersystem crossing to an excited triplet state, where it interacts with oxygen to form singlet oxygen radicals that oxidize collagen. This approach, unlike methacrylic anhydride, does not employ photoinitiators, which improves biological safety, but mechanical qualities are limited. Fan et al. discovered that RF-cross-linked collagen matrices without chemical agents achieved over 80% cell survival, but chemically cross-linked matrices exhibited cytotoxicity. Furthermore, BMSCs were encapsulated in a collagen/hyaluronic acid combination using RF, which polymerized into a gel under blue light within three minutes. ^[18]

Ionic Interaction Gelation

Sodium alginate, a natural polysaccharide polymer, may form gels in water when coupled with divalent cations like Ca²⁺, simulating extracellular matrices for cell encapsulation. However, sodium alginate hydrogels have drawbacks such as mechanical instability and limited cell adhesion sites, which inhibit biological interactions. Interpenetrating Polymer Network (IPN) technology can



address these challenges by producing 3D networks of cross-linked polymers that function as scaffolding in biological applications. Collagen, recognized for its high cell adhesion, improves the mechanical properties of the hydrogel and increases cell migration via its functional groups, hence strengthening interactions with sodium alginate. Calcium ions play an important role in modifying hydrogel stiffness; studies show that various calcium concentrations in alginate-collagen IPN hydrogels stimulate early cell proliferation and osteogenic differentiation while also allowing for stiffness-adjustable 3D cell printing.^[19]

Zhang et al. shown that alginate/collagen interpenetrating network (IPN) hydrogels are good scaffolds for cell growth. Human umbilical cord mesenchymal stem cells (hUC-MSCs) were placed onto hydrogels and used to heal skin wounds. Furthermore, several human cancer cell lines, including osteosarcoma and adenocarcinoma cells, were encapsulated to form 3D microenvironments for examining cell movement. The combination of collagen and alginate improves the preservation of biological function during fast gelation, indicating its potential in tissue engineering.^[20]

Freeze-Drying

Porous sponge scaffolds are great natural scaffolds because their interconnected structure promotes cell adhesion and migration. They are made using a freeze-drying procedure that retains collagen's triple-helical structure without using any chemicals and allows for exact control over pore features. However, they have drawbacks, such as insufficient mechanical strength for high-load tissues, quick disintegration in vivo, and susceptibility to moisture absorption, which might impair their efficacy. To keep them intact, they must be stored carefully.

To improve the mechanical strength and degradation rates of scaffolds, cross-linkers and biomaterials are employed. Khadivar et al. developed porous sponges from freeze-dried type I collagen, nano-fibrillar cellulose, and carboxymethyl diethylaminoethyl cellulose, enhancing tensile strength and stability, and incorporated BMSCs and differentiated keratinocytes for wound repair.^[21] Zhao et al. used bialdehyde carboxymethyl cellulose to cross-link collagen, creating bilayer sponges: a dense upper layer for C2C12 myoblasts and a porous lower layer for MC3T3-E1 osteoblasts.^[22]

Physical Force

Physically cross-linked hydrogels are formed through reversible molecular interactions, particularly electrostatic and hydrogen bonding, and provide biosafety by eliminating chemical crosslinking. Temperature-induced phase transition hydrogels modify hydrophilic and hydrophobic ratios to account for variations in solubility at specified temperatures, resulting in Low Critical Solution Temperature (LCST) and Upper Critical Solution Temperature (UCST). Du et al. created a rapid-sol-gel reversible thermosensitive collagen hydrogel that gelled in 60 seconds at 37 °C, encapsulating a variety of cells and increasing proliferation by tenfold over 14 days. Huang et al. improved collagen self-assembly and fiber alignment using low-temperature procedures, resulting in a fibrous scaffold with higher porosity and cellular adhesion. However, the mechanical properties of these self-assembled gels do not meet the standards for hard tissues.^[23, 24]

Table 1: Comparison between different cell-loaded collagen scaffold preparation methods

Method	Scaffold Used	Advantages	Disadvantages
Click Chemistry	Thiolated-collagen injectable hydrogel Hyaluronic acid/collagen hydrogel	More Efficient; Non-Cytotoxic; In-Situ cross linking	Natural polymers needed
Physical Force	Rapid sol-gel reversible thermosensitive collagen (RRTC) hydrogel	No chemical modification; Rapid and reversible	Temperature precision must be followed
Enzyme Cross-linking	Collagen fibril hydrogel Transglutaminase-cross-linked collagen hydrogels (Col-Tgel)	Biocompatibility; No exogenous reagent involved	Low mechanical properties
Ionic Interaction Gelation	Collagen-alginate microgels	High cell adhesion sites; Rapid	pH sensitive
Freeze-drying	Cellulose and collagen nano-scaffold	Highly tunable; No exogenous substance	Low mechanical strength; Less stability



APPLICATIONS OF CELL-LOADED COLLAGEN SCAFFOLDS

Neural Tissue Engineering

Injuries to the central nervous system (CNS) are a major global disability cause, greatly impairing quality of life, with effective treatments currently lacking. Advances in neural tissue engineering provide novel therapeutic options for neurodegenerative disorders like Alzheimer's and traumatic brain injury (TBI). A major obstacle is the limited migration of foreign cells to damage sites; nonetheless, collagen serves as a scaffold to support and guide neural cell proliferation. TBI produces secondary damage by inducing inflammation and oxidative stress, which exacerbates neurodegeneration. Collagen scaffolds boost neural stem cell (NSC) transit and proliferation, as evidenced by research that indicate improved cognitive performance and motor function recovery in animal models treated with collagen-based therapies, hence improving nerve regeneration and minimizing damage. ^[25]

The intervertebral disc consists of an inner nucleus pulposus (NP) of type I collagen and an outer annulus fibrosus (AF) of type II collagen, water, and proteoglycans. Strategies to reduce vascularization in NP tissue, such as Hu et al.'s collagen/methacrylate hyaluronic acid hydrogel, offer potential for minimizing intervertebral disc degeneration. In a rat model of IDD, this hydrogel helps to maintain disc height, protect nerve endings, and reduce vascularization and inflammation. Furthermore, injectable collagen hydrogels containing mesenchymal stem cells (MSCs) enhanced the MRI index and decreased apoptosis in AF deficiency animals. ^[26]

Spinal cord injury (SCI) frequently causes permanent disability and neurological impairments. Current treatments try to minimize edema and avoid future injury, but they are ineffective for axonal regeneration. Collagen scaffolds are being used in emerging tactics to improve cell transit and restore continuity in the wounded area, hence encouraging neural regeneration. Zou et al. found that human fetal brain neural stem cells (hbNSPCs) and spinal cord-derived neural stem cells (hscNSPCs) on orientated collagen scaffolds can improve neuronal regeneration, myelin sheath production, and synaptogenesis in rat models. ^[27] Furthermore, a three-dimensional collagen/silk scaffold that mimics the spinal cord structure promotes cell development and effectively fills damage holes, hence boosting recovery outcomes.

Skin Tissue Engineering

Skin trauma affects normal anatomical structure and function, which is commonly caused by external sources. Wound healing consists of four major stages: hemostasis, inflammation, proliferation, and remodeling. Skin tissue engineering employs three main strategies: (1) cell patches, (2) synthetic or natural polymer scaffolds, and (3) co-cultured scaffolds with cells. Collagen is essential for wound healing, as it increases cell viability and retention at the wound site, especially when paired with stem cells. Lashkari et al.'s bilayer nanofiber scaffold dressing increased healing in full-thickness wounds in rats, while Khadivar et al. used bone marrow-derived MSCs to enhance wound healing with collagen-based scaffolds. 3D MSC spheroids with collagen/chitosan hydrogels have also been found to improve diabetic wound healing by increasing vascularization and signaling. ^[21, 28]

Collagen is an efficient skin replacement matrix because to its 3D structure, fast vascularization, and proper breakdown. Liu et al. used bone marrow stem cells (BMSCs) in collagen dermal replacement scaffolds (CDRSs) to create bioactive skin substitutes that improve wound healing, especially in diabetic wounds, by modulating M1-type macrophages and promoting epithelialization, granulation tissue, and neovascularization. Xie et al. created dermal-like tissue sheets (EDSs) with MSCs in collagen/glycosaminoglycan matrices, which demonstrated better MSC preservation and activity in diabetic and healthy mice wounds than standalone hydrogels. Both collagen substitutes increased the expression of chemokines and pro-angiogenic factors, promoting chronic wound healing. ^[29, 30]

Cardiac Tissue Engineering

Collagen types I and III make up the majority of the extracellular matrix (ECM) of the human heart, which is essential for giving cardiac tissues flexibility and structural stability. One of the main causes of death, myocardial infarction (MI), is caused by blockage of the coronary arteries, which causes the heart tissue to necrotize. Restoring blood flow is the main objective of current treatments, but myocardial regeneration—a crucial objective in cardiac tissue engineering—is not adequately encouraged. In this field, conductive materials are crucial, yet traditional electroactive biomaterials frequently have compatibility issues. Collagen mimics the extracellular matrix (ECM) environment for cardiomyocyte development by acting as a scaffold. Research demonstrates that hydrogels containing conductive elements, such as PEDOT-PSS, can improve cardiomyocyte contractility and myocardial protection in infarcted mice, indicating their promise for treating MI. ^[31]

A key tactic for producing regulated 3D tissue settings that resemble natural tissues has been the development of 3D printing technology in recent years. Human ventricular cardiomyocytes (hCMs) and cardiac fibroblasts (hCFs) were encapsulated using



collagen/methacryloylated gelatin hydrogel as a bio-ink by Kim et al. [32] They showed that 3D bioprinting produced a more porous hydrogel structure, improving cell viability in comparison to manual inoculation. Rats with acute myocardial infarction (AMI) showed significant improvements in graft survival, vascularization, and cardiac function after receiving 3D-printed patches. However, the mechanical modulus of collagen makes it difficult to encapsulate cardiomyocytes. In order to overcome this, collagen-based cardiac constructions can be precisely designed using the Freeform Reversible Embedding of Suspended Hydrogels (FRESH) technique.

Bone/Cartilage Tissue Engineering

In addition to being an essential structural support system for the human body, bone tissue has the innate capacity to fix small flaws in itself. Larger bone abnormalities brought on by a variety of illnesses, however, necessitate medical attention; bone grafting and surgical repair are typical methods. With an emphasis on characteristics like osteoinductivity, osteoconductivity, and biocompatibility, scaffolds designed to improve bone regeneration have been developed as a result of recent developments in bone tissue engineering. A crucial part of these scaffolds is collagen, which promotes stem cell activity and aids in bone production. Innovations that have improved mechanical stability and osteogenic differentiation include the use of collagen in conjunction with ceramic materials and synthetic polymers. Furthermore, cartilage repair techniques emphasize how important collagen is in creating the ideal conditions for stem cell development. However, the paucity of bone defect models makes many studies clinically irrelevant. [33, 34]

Liver Tissue Engineering

The liver has a remarkable ability for regeneration and is necessary for many processes. However, serious injuries might impair this capacity, resulting in acute liver failure or end-stage liver disease, for which in situ transplantation is frequently the only course of treatment. A viable solution to lessen the consequences of immunosuppression and transplant shortages is liver tissue engineering. Liver tissue can be rebuilt by seeding cells onto scaffolds made of biodegradable polymers. Collagen is essential for giving hepatocytes a supportive microenvironment that promotes tissue regeneration. In one study, a favorable environment for hepatocytes and other cell types was effectively generated using collagen bio-ink, leading to enhanced biological capabilities. In contrast to conventional membranes, a bionic membrane containing collagen and chitosan was shown in another study to improve hepatocyte proliferation and liver-specific activities. [35, 36]

CONCLUSIONS

Collagen, which makes up around 25% of all body protein, is an essential structural protein in the extracellular matrix of vertebrates. Its triple-helical structure offers flexibility and tensile strength for supporting cells. Coagulation, wound healing, and inflammatory processes all depend on collagen. By interacting with cellular integrins, it improves signal transmission and affects cell processes like adhesion and proliferation. The mechanical qualities of collagen scaffolds used in tissue engineering, which can successfully repair tissues like skin and bone, are enhanced by a variety of cross-linking techniques. To increase their effectiveness, biofunctionalized scaffolds including growth hormones and antibacterial components have been developed. Despite their potential, there are still issues such as possible biological responses from other materials. Optimizing collagen scaffolds for clinical use in regenerative medicine requires ongoing study.

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