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Polymeric Scaffolds Used as Prosthetics for Regenerating Tendons

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Abstract

Certain injuries such as torn tendons may require a prosthetic in order to heal properly. The materials that are used for the prosthetic would be synthetic or natural polymers that need to be both biodegradable and flexible. Tendon tissue engineering (TE) looks into polymeric scaffolds as a means of tendon and ligament prosthetics. Some natural polymers used are collagen derivatives, silk, and polysaccharides that provide different properties with beneficial bioactivity. Synthetic polymers are a stronger and more reliable alternative to natural polymers for building a scaffold. These synthetic polymers are polyesters such as polyglycolic acid (PGA) and polylactic acid (PLA) that are biodegradable but unable to promote cell adhesion. Polyhydroxy esters like copolymer poly (lactic-co-glycolic acid) (PLGA) is another synthetic polymer, that has an appealing degradation rate via hydrolysis but needs to be combined with PLA to help slow its degradation. Another synthetic polymer, polycaprolactone (PCL), has slow degradation but poor cell adhesion, so it is combined with collagen. Certain techniques allow the scaffold to be formed into mesh, film, hydrogel, foam, and sponge. Electrospinning is one technique that charges a polymer solution to form a fiber to fit the specifics of the ECM. Drying technologies make the scaffolds porous and dehydrated, improving their degradation rate. A modern technique on the rise is 3D-printing, to make a repeatable and precise design. It is highlighted that TE scaffolds are seen to be a more viable option than autografts and allografts, with hybrid scaffolds being made of both natural and synthetic polymers to produce desired characteristics.

Keywords: tissue engineering (TE), natural polymers, synthetic polymers, polymeric scaffolding

Introduction

The human body itself is very powerful in its natural regenerative abilities, be it recovering from a sickness, healing a wound, or repairing an internal injury. But many times, these natural abilities are not enough to fix the problem. When the autonomic nervous system encounters an issue that cannot be handled naturally, medicine can be used to help with the problem. An example of this would be a broken bone or torn tendon that requires surgery to heal correctly. Many times, these surgeries require some kind of prosthetic with certain elements such as biodegradability or flexibility to be put in place.[1,2] This is why the engineering of these prosthetics is so important. The main components for such prosthetics typically include synthetic polymers such as nylon, fiberglass, carbon fibers, polyester, acrylic, and epoxy resins, along with other natural polymers.[3] Recently, there is an interest in the biomedical community to push forward the agenda of research in tissue engineering (TE), and more specifically in tendon tissue engineering. Tendon and ligament injuries are very frequent and require additional aid in the healing process due to their poor regenerative capacities.[2,4] Polymeric scaffolds can be used as prosthetics to initiate and improve the healing process within the tendons and ligaments. Scaffolds are domains of biomaterials intended to aid, refine, and retain the properties of the native tissue.[5] Scaffolds can be made up of natural or synthetic polymers through various techniques.[1,2,4,6] Future research seeks to improve upon the healing capabilities and processing methods of using polymers within these scaffolds.

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Background of Tissue Engineering

The use of prosthetic devices has been present in the world since 3000 BC.[7] The science behind prosthetics is always evolving and improving. The earliest prosthetics were made of simple natural materials such as wood or wax, while more recent prosthetics are made of 3D printed polymers.[7] With many uses for prosthetics in different parts of the body, new technology and medicine points to research on regenerative prosthetics for the tissues in the musculoskeletal system. The value and versatility of tissue engineering (TE) make it vital to the production of prosthetics in biomedicine. TE, more specifically for tendons and ligaments, is very important because of the frequency at which such injuries occur. Tendons and ligaments take enormous loads of force and are prone to injury for their poor vascularity and low oxygen/nutrient requirements. This explains why tendon injuries account for more than 32 million injuries yearly in the US.[2,8] The most common surgical practice to repair injured tendons is the transplantation of tissue from another part of the body (autograft) or a donor (allograft).[9,2,10] Autograft and allograft transplants are very successful in mechanical strength and rehabilitation in the short-term. As for the long-term, studies have shown them to eventually cause infections or immunogenic responses, that is a substance causing a reaction from the immune system, in the surrounding tissues and often result in recurrent injury.[2,8] The use of scaffolds from TE is a more promising alternative made of biomaterials that are compatible with cells.

In the formation of scaffolds, many biological factors must be considered. The main goal of a scaffold is to be compatible with the native tissue that it is repairing. This is done by mimicking the extracellular matrix (ECM) of the native tissue.[1] The ECM is the complete description of the three-dimensional structural mechanics and biochemistry of the macromolecular network that makes up the tissue[10]. In addition to the scaffold having all the

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characteristics of the tissues' natural ECM, they must also be biodegradable. This needs to be at a rate in which there is full regeneration of the tissue through cell growth, and adhesion from the stem cells or other specialized cells within the scaffold[1]. The degradation rate of a polymer is vital and can change depending on the polymer's molecular weight and crystallinity.[2] The biodegradable materials that inhabit all of these qualities include many synthetic and natural polymers and are therefore used in the creation of scaffolds.

Natural Polymers

The most simple and obvious way for a scaffold to interact with cells and the rest of the body is to make it out of the same natural materials as the injured tendon. The composition and structure of tendons are primarily comprised of the main component of the ECM, which is type 1 collagen.[1,9] Because of this, many natural scaffolds are made with collagen derivatives, which are hydrophilic polymers that promote cell growth and cell adhesion, as it was among the first natural materials used for scaffolds.[1,2] Purified collagen derived from animal tissue must undergo crosslinking in order to rid it of disease, remove foreign antigens, improve its strength, and decrease the degradation rate.[2] Crosslinking can be done chemically or by irradiation to form chemical bonds between polymer chains. Once crosslinked, this ensures greater stability at higher temperatures, along with many other desired effects that can be shown in Figure 1.[11] One study conducted in 2005 demonstrated biodegradability as an additional characteristic when they found the complete resorption of a collagenous scaffold in the knee of a rabbit after 6 weeks.[12] But even after the crosslinking, collagen has poor mechanical and regenerative properties for the tendon, so improved strategies and other materials are being sought after.[2]

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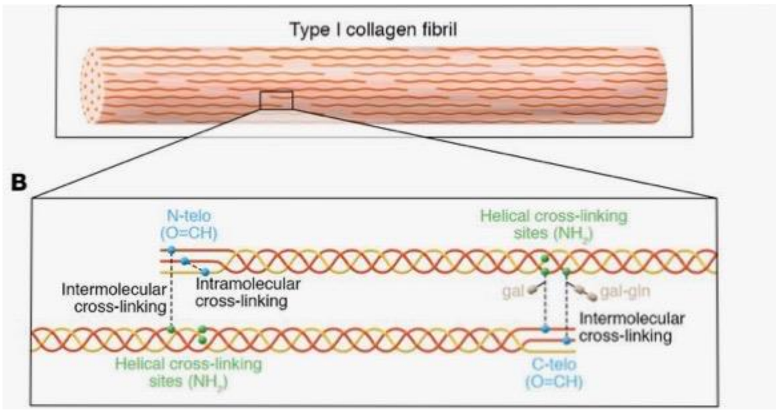

Figure 1 – Crosslinking of Type 1 Collagen

One alternate natural polymer with superior toughness that can easily be constructed in many forms is silk.[9,2] Silk provides low immunogenicity and biocompatibility with cells in vivo and in vitro.[9] A study conducted on mountain sheep in 2016 using braided silk fibers to produce the scaffolds, successfully stimulated ACL regeneration in vivo and resulted in improved fibroblast adhesion with higher cell density and collagen production.[13] Silk has surface amino acids for cell adhesion and degrades slowly through proteolysis (Figure 2), which is the breakdown of its proteins to amino acids by enzymes.[4] Silk is widely used as a biomaterial because of these features and its exceptional tensile strength.

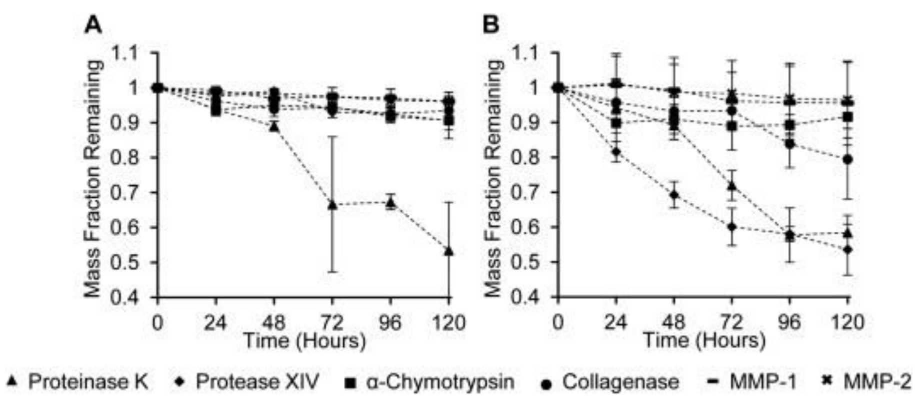

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Figure 2 – The rate of degradation of silk nanoparticles proteolysis compared to other enzymes

Another natural polymer option for tendon TE is polysaccharides. They are generally used in the regeneration of hard tissue.[1] As shown in Figure 3, hyaluronic acid is an anionic linear polysaccharide that is found in all soft tissue and is responsible for the maintenance of the ECM.[2] Hyaluronic acid is not immunogenetic, but it supports cell adhesion/growth, and is anti-inflammatory. However, due to its short degradation time, modifications are needed to improve it as a biomaterial.[2] A cationic polysaccharide, chitosan, has great biocompatibility to produce scaffolds when typically combined with alginic acid and hyaluronic acid. These form poly-ionic complexes for scaffolds with desirable properties because of their opposite charges.[2]

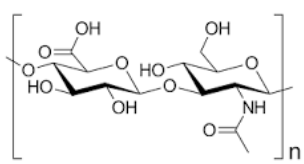

Figure 3 – Structure of hyaluronic acid

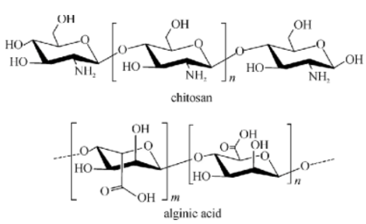

Figure 4 – Structures of chitosan and alginic acid

Synthetic Polymers

Synthetic polymers are a stronger, more reliable alternative to natural polymers for building a scaffold. Many of these polymers are polyesters like polyglycolic acid (PGA) and polylactic acid (PLA) that also have the beneficial property of biodegradability.[1] Due to their flexibility and strength, synthetic polymers are very appealing to TE. Synthetic polymers are inexpensive to produce and easy to mold into various forms. They can also be non-toxic and processed under mild conditions to make them compatible with cells.[9] Still, synthetic polymers are typically unable to promote cell adhesion at a high degree, thus they usually require specific coatings.[1,9] Polyesters including polycaprolactone (PCL), poly(lactide-co-caprolactone) (PLCL), poly(lactic-co-glycolic acid) (PLGA), as well as the aforementioned PGA and PLA are common materials for scaffold production in TE.[2]

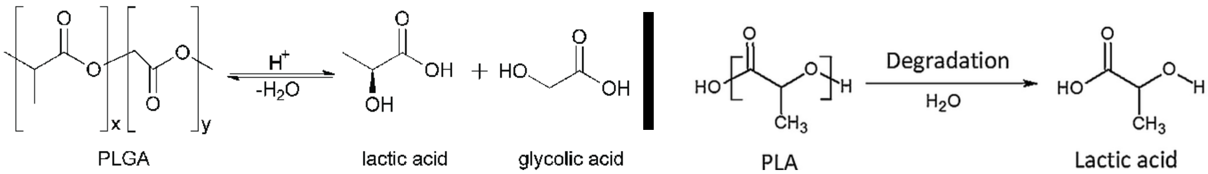

Figure 5 – Structures and hydrolytic reactions of PLGA and PLA

Polyhydroxy esters are at the forefront for synthetic polymers used in tendon TE and are among the best in degradation rate because they degrade by hydrolysis.[9,2] These polyhydroxy esters include the copolymer poly (lactic-co-glycolic acid) (PLGA) with its flexible and reabsorbing qualities.[2] Since its monomers are lactide and glycolide, PLGA undergoes biodegradation by chemical hydrolysis of the hydrolytically unstable ester bond and produces lactic acid and glycolic acid, which are naturally removed by the metabolic pathways of the body.[2] Because of this swift biodegradation, PLGA is unable to stay intact long enough to promote the regeneration of the tendon and is therefore combined with other polymers like polylactic acid (PLA).[2] PLA has a much slower degradation rate, as it undergoes hydrolytic scission with a product of lactic acid which is released from the body through respiration as CO_2.[2] Polycaprolactone (PCL) is another synthetic polymer with a slow degradation rate and high tensile strength but with poor cell adhesion due to its hydrophobicity, so it is usually combined with chitosan or coated with collagen.[2]

Techniques

A big part of a scaffold's success relies on the methods and techniques behind how the biomaterials of the scaffold are formulated and concocted in the creation of the scaffold. From these techniques, polymers can be configured into various forms like mesh, film, hydrogel, foam, and sponge.[3] One popular technique that is used in the formation of many scaffolds is electrospinning. In electrospinning, a polymer solution is charged with an electric potential and forms a fiber that can be modified in its composition, diameter, and alignment to best fit the specifics of the target ECM.[1,9] In this process, crosslinked natural and synthetic polymers are often blended into nanofibrous matrices which can be knitted or braided together for maximum tensile strength and flexibility.[1,9,2] For there to be promotion of cell proliferation and nutrient transport, drying technologies are used on the polymers to make the scaffolds porous. Drying also causes a polymer that is too hydrophilic to become dehydrated, making it more stable in aqueous solutions, and therefore improving its degradation rate.[6] Typical for hydrogels and sponges, freeze-drying with ice crystals can induce phase separation in a polymer solution to make the polymer porous and aqueous stable.[1,9] 3D-printing is another more modern technique used in TE that is able to make repeatable and precise designs on the architecture of a scaffold on a micro and macro scale.[2] As shown in Figure 6, a study done in 2016 was able to create a scaffold made of collagen-glycosaminoglycan and acrylonitrile butadiene styrene using 3D-printing, reporting on its success of biocompatibility and tensile strength.[8] Although 3D-printing is a very precise and efficient technique to create scaffolds, it is not widely used because it is fairly new with much more research to be done, but it holds a bright spot in the future of scaffold production in TE.

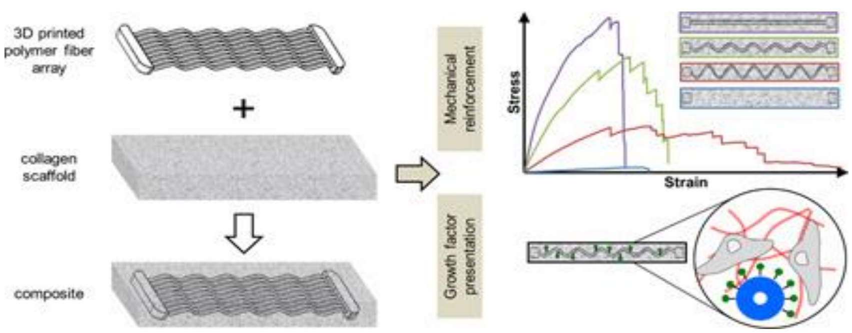

Figure 6 – Theoretical formation of a 3D printed scaffold

Conclusion

With the ongoing demand of finding new ways to repair common reoccurring injuries, especially for tendons and ligaments, polymeric prosthetics are there for temporary support and to develop regeneration. Polymers play a key role as the biomaterials of choice for scaffolds in tissue engineering. Scaffolds can be made of natural or synthetic polymers that are typically combined to form hybrid scaffolds with the great bioactivity of the natural polymers and the exceptional mechanical properties of synthetic polymers. The methods by which these polymeric scaffolds are created pose an important role in the success of the scaffold. Scaffolds are a better alternative to autografts or allografts due to them allowing your body the

chance to regenerate on its own. With the manipulation of fiber orientation, the required three-dimensional properties of the extracellular matrix and native tissues can be achieved. Research will continue in finding what combination of polymers and how they are best formed to make the most reliable and regenerative scaffold.

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