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Synthetic Materials Used for Cartilage Regeneration in Recent Decade

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Abstract:

Cartilage injury is considered the major cause of joint pain, swelling and dysfunction. Due to the cartilage tissue's limited repair capacity, it's very urgent and crucial to develop and investigate biomaterials to improve effective cartilage regeneration. Over the past decade, researchers focused of the design and preparation of a variety of synthetic materials. There synthetic scaffolds are expected to provide a favorable cellular microenvironment which is beneficial for cartilage regeneration. This review comprehensively reviews the major synthetic materials that have been recently applied in cartilage regeneration engineering, including a variety of polymers and a number of 3D printed materials. These materials have unique physicochemical structures and properties that can provide biocompatible three-dimensional porous structures, mimic the extracellular matrix environment in vivo, and promotes cell adhesion, proliferation, and differentiation. These properties all guide the orderly regeneration of cartilage tissues. Especially through the composite with bioactive molecules, nanomaterials, etc., these materials can also realize the controlled release of biological signals and precisely regulate cell behavior. In addition, by compositing natural polymers with synthetic polymers gives the hybrid scaffolds good bioactivity, it will also enhance their mechanical properties as well as the scaffold elasticity. These techniques allow researchers to develop the most ideal scaffold that perfectly mimics the natural cartilage environment.

Keywords: Cartilage; osteoarthritis; cellular environment; biomimetic scaffold; 3D printing; hybrid/composite scaffold.

1. Introduction

In the recent decades, cartilage injury is becoming a more and more commonly discussed topic by people and researchers. An untreated cartilage injury could easily lead to the development of osteoarthritis, which is a degenerative disease that would worsen as time progresses [1]. According to Medical News Today osteoarthritis affects around 500 million people worldwide which is about 7% of the entire population.

Unlike other tissues in the human body, cartilages lack blood vessels in it, which means that when cartilage is damaged, it's almost impossible for it to regenerate by itself due to the avascular nature of the cartilage tissue.

There are usually two treatments available for patients who has cartilage injury, nonsurgical and surgical options. nonsurgical treatments such as resting, applying ice to joint, viscosupplementation etc. are used to prevent further degeneration and damage to the cartilage. However, although these treatments could make life easier for patients by reducing pain and enhancing strength as well as flexibility, nonsurgical treatments cannot regenerate the damaged cartilage. The surgical treatments is often the best and only way to repair a damaged cartilage. However, these surgeries could not treat the extensive loss of cartilage caused by the disease osteoarthritis, they are mainly used to treat damaged caused by sport and acute injuries. One of the most common surgical treatments nowadays used for cartilage is called the Matrix Autologous Cartilage Implantation (MACI). This procedure involves removing part of patients' healthy cartilage and sending this tissue to the laboratory. In the laboratory, the chondrocytes are harvested and grown over several weeks on a collagen membrane on scaffold, which would be later inserted back to the area with damaged cartilage, allowing the chondrocytes to form new cartilage [2].

Materials used for these scaffolds could be divided into three main categories. Biological materials, synthetic materials and hybrid materials which is a combination of biological and synthetic materials. An example of a native biological materials could be collagen, the reason why biological materials such as college are chosen to produce scaffolds is because of its high tissue compatibility, little toxicity, and its nature of easy biodegradation. However, here are some key limitations of these biological materials that doesn't make it a perfect material for making cartilage regenerating scaffold. These drawbacks include weak mechanical properties and unpredictable rate of degradation. Synthetic materials on the other hand could be easily modeled and designed by researcher, meaning that mechanical structure and degradation rate could be controlled and modified to the benefit of the researchers. Some of the most widely used and well-known synthetic materials are poly(lactic-co-glycogen) (PLGA) and polymer of lactic acid (PLA). However, these synthetic materials also have their drawbacks too. Synthetic materials are very expensive, some have low cell adhesive ability and it will also produce acidified degradation product which is like to cause an inflammation reaction [3, 4].

The paper will give a brief overview of the synthetic materials used in cartilage regeneration. Section 2 discusses about the extracellular matrix and what environment is needed for the chondrocytes to grow. It then goes on talking about how synthetic materials could imitate the cellular environment. Section 3 will introduce the concept of hybrid material scaffolds, and the synthesis and fibrin techniques would be explained. Section 4 talks about the future of various materials and scaffolds and ways to improve.

2. Cellular Environment

Cellular environment is one of the most important factors effecting cell proliferation and regeneration. There are many ways how cell proliferation could be affected by the environment of the cell, for example, research shows that upregulation of the p53 and p21 protein causes the reduction cardiomyocyte proliferation and delays the cell cycle process in Lmna mutant mouse. This study suggests that cell proliferation could be restricted through the upregulation of cell cycle regulatory proteins such as p53 and p21 [5].

Other ways that cellular environment could affect cell proliferation is the mechanical factors of the extracellular matrix. Matrix stiffness could regulate the proliferation of cell through controlling the cyclin D1 protein as it essential for the progression from G1 to the S phase in the cell cycle. By increasing the matrix stiffness, the expression of cyclin D1 is promoted through various pathways, this stimulates Rb phosphorylation and S phase entry. On the other hand, when the matrix softens, the cyclin D1 is barely or not expressed at all, which may cause the cell cycle to stop and inactivate [6].

Cell-to-cell communication is another very critical way that regulates the cell proliferation in your body. In cells, cell-to-cell communication's major function is to help the cell's homeostasis and regulate the cell in order to grow and divide when it's appropriate. There are several ways in which cell-to-cell communication could happen, direct contact between the cells or by secreting soluble signaling molecules such as growth factors, cytokines and chemokines. These signals are what controls the cell's fundamental cell processes including cell proliferation, cell-to-cell communication could also transmit signals that encourages cell division in neighbouring cells. An example of this would be tumor cells, they invade the normal communication pathways and releases a huge amount of signals such as growth factors which would cause neighbouring cells to replicate uncontrollably eventually forming cancer cells [7].

3. Biomimetic Scaffolds

The cellular environment could affect the process of cell proliferation significantly. It is crucial for scientists to find a way to mimic the cellular environment in the scaffolds used to regenerate cartilage since they need to grow the chondrocytes in the scaffolds. So biomimetic scaffold is developed, biomimetic scaffold is synthetic scaffolds which is engineered to mimic key structural and functional features of the natural extracellular matrix for a better and more effective way to support cell regeneration. The synthetic biomimetic scaffolds are usually made by biodegradable polymers such as PLA [8].

The fabricating techniques of these scaffolds are also very important. There are two major categories of fabricating techniques used to make synthetic materials, conventional and advanced. The main conventional fabrication methods is the solvent casing/particle leaching methods, the first step of the process is preparing the polymer solution, the solution is prepared by dissolving polymers in a volatile organic solvent, something like chloroform or dichloromethane. Then porogens are dispersed into the solvent and mixed, the best porogen being sodium chloride. After that the mixture is casted into a mold and left to evaporate which will turn into a material made up of polymer matrix and porogens. Lastly the porogens were leached out from the matrix, leaving behind pores of various sizes. This method of fabricating scaffold is very limited due to how long it takes, it also limits the scaffold up to 3mm think and it is also hard to completely remove the residue on the scaffold. This is why the advanced fabrication method caught everyone's attention and is being used more frequently in the past decade. Amongst all of the advanced fabrication methods, 3-D printing which is a computer-aided design (CAD) technology has been used to manufacture scaffolds a lot due to its precise and easy nature. The 3-D printing techniques could be classified into three types: i) laser-based 3D printing which includes in particular stereolithography (SLA), selective laser sintering (SLS), digital laser printing (DLP); ii) extrusion-based 3D printing which includes fused deposition modeling (FDM), and iii) ink-based 3D printing which includes in particular ink jet printing (IJP), and aerosol jet printing (AJP). Extrusion-based 3D being the most well-known and popular amongst the three. Compared to the conventional fabricating techniques, the advanced 3D printing technique could customize the scaffold into desired shape and proportion [9].

Synthetic biomimetic scaffolds try to replicate the complex cellular microenvironment inside cartilage tissue as much as possible. So, they create a suitable environment and condition for cell attachment, proliferation and differentiation. The synthetic biomimetic materials do this by replicating the mechanical and also the biological properties that's present in the cell's environment. In terms of mechanical properties, cartilage tissue is very strong but flexible at the same time. Therefore, synthetic scaffolds need to be made of materials with tunable mechanical properties, such as hydrogels or composites, in order to replicate this property, such design ensures that the scaffolds are designed to withstand physiological loads while providing a suitable environment for chondrocyte growth and matrix deposition.

Beside the mechanical properties, the biocompatibility and the biodegradability are also important factors to think about when designing artificial scaffolds. The use of biodegradable materials like polylactic acid (PCL) or PLGA to manufacture scaffolds ensures their degradation over time, gradually replacing them with newly generated cartilage tissue.

4. Hybrid/Composite Scaffolds

In order to mimic the natural cartilage environment, researchers often integrate bioactive molecules such as growth factors, cytokines or ECM components into artificial scaffolds, which can promote chondrogenesis, regulate cellular behaviors and tissue integration. The procedures optimize the scaffold to work in a natural biological environment. Furthermore, surface modification and integration of cell adhesion motifs (e.g., RGD peptides) are also effective strategies to enhance scaffold-cell interactions, and this design enhanced cell attachment, spreading, and proliferation on the scaffold surface and mimicked the interactions between the cells and the natural ECM.

As mentioned previously, the mesenchymal stem cell that forms new cartilage requires scaffolds that has both mechanical strength and elasticity. The scaffold would have to be strong enough to support the joint load caused by body weight and would also have to support cell growth. By blending different synthetic polymers, the mechanical properties of scaffolds can be adjusted to better mimic the mechanical behaviour of a natural cartilage. A good example of this would be blending PLA with PCL. Polylactic acid is a biodegradable aliphatic polyester, this means that it will degrade naturally with is idealistic for a scaffold. As the new cartilage tissue grows, it will gradually replace the scaffold and the scaffold needs to degrade. However, it doesn't quite meet the requirements to make a biomimetic scaffold as it is brittle, has little resistance to heat and also has limited gas barrier. On the other hand, PCL is ductile and has high impact strength. By blending these two synthetic materials together, they could modify the polymers into a well-rounded polymer with balanced properties [10, 11].

5. Future Developments

5.1 The Problem of Immune Response

Despite significant progress, synthetic scaffolds still face a number of challenges in clinical applications, among which immune rejection is a major obstacle. Not a single synthetic material guarantees that it will not cause inflammation or other responses outside of the body. Not even the more biocompatible synthetic materials. The stent degradation products and alleviation of inflammation are also issues that need to be focused on. In order to improve, it's necessary for researchers to develop a new and more biocompatible materials in the near future. They have to explore and investigate anti-inflammatory and immuno-modulatory strategies to decrease the probability that the body rejects the synthetic scaffold.

5.2 Durable Materials

Cartilage repair processes often take a long time, so scaffolds need to have good durability to maintain structural integrity while adequately supporting cells and neoplastic tissues. By enhancing the mechanical strength of the material and slowing down the degradation kinetics are the keys to achieving long-term stability of scaffolds. Several studies have attempted to improve the durability of polymer scaffolds using inorganic nano-reinforced materials (e.g., hydroxyapatite, graphene, etc.).

5.3 Personalized Materials

Everybody is a unique and very different individual. Thus, a personalized stent material and design may provide better outcomes for certain patients. The 3D printing technology has the great potential to create personalized stents. The 3D printing technology would allow us to customize the shape and internal structure of the stent based on the patient's bone/leg shape. Also, the integration of a patient's own cells and biomolecules could be the answer for a truly personalized treatment.

6. Conclusion

Synthetic materials for cartilage regeneration have experienced great progression in the last decade. Through discovering more about the cellular environment, biomimetic scaffolds, creating different composite scaffolds, etc., researchers have been exploring and innovating, bringing new hope to cartilage regenerative treatments.

The cellular environment is a key factor that affects the cartilage tissue's proliferation and regeneration. Mechanical factors, active and inactivate proteins and cell-to-cell communication could all become factors that influence cartilage regeneration. So it is crucial to find a way to accurately mimic the natural environment in order for cartilage treatment to be successful. This is the reason desiging and preparing biomimetic scaffolds has been so valued by researchers. Biomimetic scaffolds has become a very hot research topic in recent years. By simulating the composition and structure of natural cartilage, biomaterial scaffolds with similar mechanical strength, modulus of elasticity and hierarchical porous structure can be developed to better simulate the microenvironment of natural cartilage. Thus, guiding and promoting the growth and differentiation of chondrocytes on the scaffold. In addition, composite scaffolds made of natural bioactive molecules (e.g., growth factors, extracellular matrix components, cytokines etc.) mixed with other synthetic materials are also a hot area of current research. This kind of composite scaffold made has better and well-rounded features than other natural or synthetic scaffolds. The composite/hybrid scaffolds could increase the success rate for cartilage regeneration greatly. They would also optimize the efficiency of cartilage tissue regeneration, saving both time and energy.

With the continuous development of materials science, biomedical engineering, and cell biology. The application of synthetic materials in the field of tissue engineering and regenerative medicine will surely be discovered more thoroughly and extensively. However, in the present, cartilage regeneration is far from perfect. The problem of natural immune response caused by the body is still not solved, the long-term durability and stability of scaffolds are yet to be improved, and hopefully in the future we would be able to personalize scaffolds so every patient could have customized scaffolds. There's still a long way for us to go with the synthetic materials used for cartilage regeneration.

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