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Review

Hybrid hydrogels for bioink development and potential use in dental tissue engineering

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Abstract: One of the emerging problems in medicine and dentistry today is how to replace and regenerate damaged tissue. Currently used implants are inert and need to be replaced after a certain period. Therefore, the aim is to develop a bioactive multicomponent material that can promote tissue regeneration. Hydrogels are the focus of research in this field because of their similarity to the natural extracellular matrix and their good biocompatibility. Nevertheless, hydrogels often have insufficient mechanical properties for handling and implantation. Therefore, methods of hydrogel reinforcement are developed by adding at least one phase to obtain hybrid hydrogels. There are various methods to reinforce hydrogels, such as functionalization, interpenetrating networks, nanogels, nano-engineered ionic covalent entanglement, etc. The obtained hybrid hydrogel can be used to develop a bioink, a biocompatible and biodegradable material mixed with cells that has suitable properties for 3D bioprinting. The 3D bioprinting method is used to obtain scaffolds of the desired shape and size. Hybrid hydrogel-based 3D printed scaffolds have shown great potential in biological assessment to promote the regeneration of a variety of tissues.

Keywords: hybrid hydrogel, bioink, tissue engineering

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Introduction

Due to diseases and aging, it has become necessary to replace damaged tissues. Since there are many health problems associated with autologous, homologous, or xenologous grafts, tissue engineering has emerged as a promising solution. Its main goal is to develop a biocompatible, biodegradable, and bioactive scaffold with the desired microstructure [1]. Subsequently, a conventional strategy is to seed cells on the surface of the scaffold, but this has been shown to result in a large loss of cells. Mixing the cells with the biomaterial to form a bioink is considered a better method [2].

Achieving specific microstructure of tissue constructs is one of the challenges introduced to scientists. So far, several methods have been developed to produce microstructures. Some of them are electrospinning, freeze-drying, and self-assembly, but the use of 3D bioprinting has shown promising results in achieving a specific porous structure at the microscopic level [3]. Bioprinting is a novel technology that combines the method of 3D printing complex structures with bioinks. It involves using a previously created file with information about the specific shape and size, and deposits material to the surface layer by layer [4]. There are several bioprinting technologies: extrusion, inkjet, and laser-assisted

bioprinting. For each bioprinting technology and specific application, it is important to fine tune the properties of the bioink so that it is suitable for the bioprinting process [5]. Bioinks are cell-containing biomaterials that are biocompatible, have good mechanical properties, and protect the cells from shear stress during the printing process [6].

This field has attracted much attention in recent decades because it allows precise control of the distribution of cells and biomaterials in a complex microstructure that mimics the natural extracellular matrix (ECM). Given the shortage of bioinks that meet the above requirements, it is of great interest to develop new biomaterials with advanced properties. Hydrogels are being extensively studied as scaffolds for tissue engineering purposes. Similar to the natural ECM with large biomolecules in the extracellular fluid, hydrogels consist of hydrophilic polymer networks and large amounts of water [7].

The aim of this article was to summarize the current findings and approaches in the development of hybrid hydrogels as bioinks, their use in 3D bioprinting, and their potential application for dental tissue engineering purposes.

Hydrogels

The most used materials for bioink development are the hydrogels. They are materials formed by hydrophilic polymers that crosslink into networks and swell with a high percentage of water (> 70% of the total polymer mass) [8]. The polymer chains in hydrogels can be linked by physical or chemical crosslinking. Physical hydrogels are obtained via physical interactions such as electrostatic or hydrophobic interactions, hydrogen, or coordination bonds. They are mechanically weak, have plastic flow, respond to stimuli such as temperature, pH, type of solvent or change in ionic strength, and are therefore reversible and unstable gels. Chemical hydrogels consist of covalently crosslinked polymers and have good mechanical stability. The disadvantage of chemical crosslinking is the use of initiators, chemical crosslinking agents, which are often toxic [9]. Based on the method of preparation and the polymers that form the networks, hydrogels can be classified as homopolymers of only one type of monomer, heteropolymers of two or more type of monomers, hybrids of chemically different macromolecules, interpenetrating polymer networks (IPNs), or composites of organic and inorganic components [10]. Hydrogels can be of natural origin such as cellulose, chitosan, pectin, collagen, gelatin, etc. or synthetic such as polyethylene glycol (PEG), poly(lactic acid) (PLA), poly(ε-caprolactone) (PCL), poly(vinyl alcohol) (PVA), etc. [11]. The choice of polymers, their composition and network structure depends on the desired properties of the hydrogel and its purpose [9], [12].

Hybrid hydrogels

Hybrid hydrogels consist of macromolecules and sometimes particles with chemical, functional, and morphological differences, i.e combine the good properties of all the phases in the hydrogel. Natural biodegradable and biocompatible polymers are often combined with mechanically stable and chemically tunable synthetic polymers. Natural polymers provide biocompatibility and cell adhesion sites, while synthetic polymers provide mechanical stability and possible chemical modification of properties. In this way, a material with improved properties is obtained without chemical reaction [13]. It is known that hydrogels obtained from natural polymers rarely have sufficient mechanical properties for bioprinting due to presence of only physical crosslinking. Chemically crosslinked hydrogels are randomly crosslinked in a single network, and when forces are applied, heterogeneity in mechanical properties occurs due to the different density of covalent bonds between polymer chains. Therefore, it is necessary to reinforce hydrogels to improve their mechanical stability. There are several methods for reinforcing hydrogels and thus obtaining hybrid hydrogels [7].

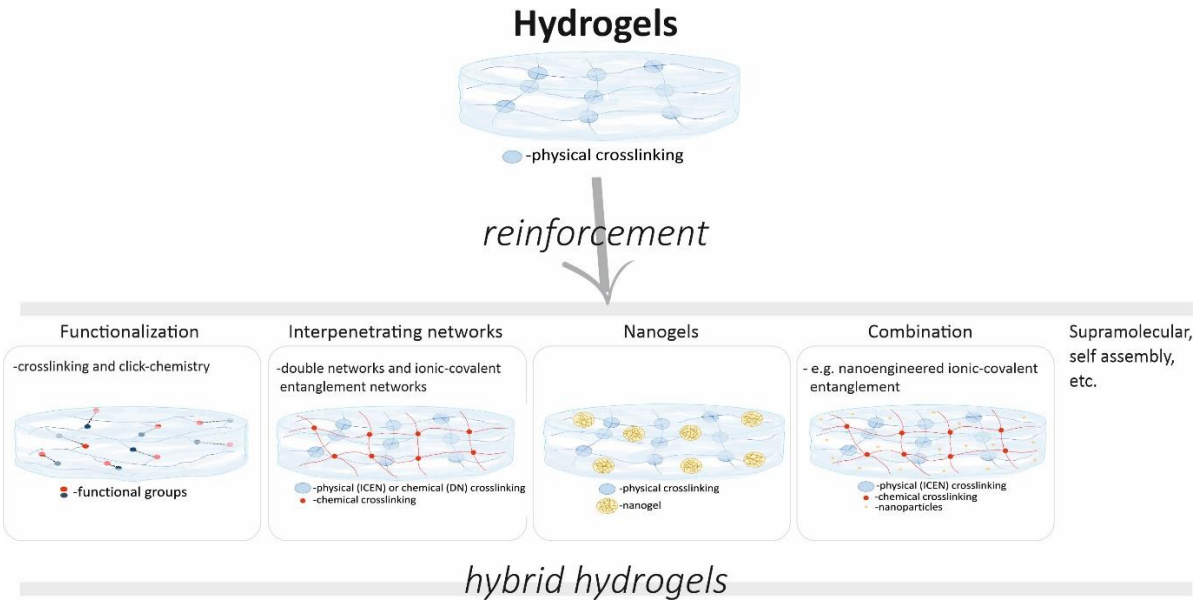

Figure 1. Methods of hydrogel reinforcement

Functionalization of hydrogels

One way to reinforce natural polymer hydrogels that are physically crosslinked is through functionalization and covalent crosslinking. In this way, the mechanical properties are less dependent on the environment and better overall. Other properties can also be improved through functionalization, such as degradation or cell adhesion. Natural bioinks that have already been functionalized include gelatin, collagen, hyaluronic acid, and alginate [14]. Klotz et al. functionalized gelatin with methacrylic anhydride to form methacrylate functional groups that covalently bind in the presence of UV irradiation and initiator. The hydrogels obtained in this way were more resistant to degradation and had higher fracture energy [15]. Nichol et al. also methacrylated gelatin. It was shown that the degree of functionalization and crosslinking had a proportional effect on the mechanical properties and swelling. In addition, this material exhibited high printing fidelity while seeded cells adhered to the material and proliferated [16]. Another way to functionalize natural polymers is through click chemistry, a series of selective reactions that occur under mild conditions. Hydrogels that have been functionalized by click chemistry exhibit more homogeneous crosslinked networks and are therefore more fracture resistant [17]. Zhang et al. prepared a collagen hybrid hydrogel with aldehyde-dextran via Shiff base reaction. The obtained hydrogel had 20 times higher compressive strength compared to a pure collagen hydrogel [18]. Lueckgen et al. coupled alginate with norbornene groups using carbodiimide chemistry, where alginate was peptide crosslinked by a thiol-ene reaction in PBS. The results showed that the degradation rate can be modified by the type of crosslinker and that the obtained hydrogel represents a suitable microenvironment for cells [19].

Interpenetrating networks

Interpenetrating networks (IPNs) are hybrid hydrogels consisting of two polymer networks connected by covalent, ionic, or both types of bonds. Depending on the type of bonding between the networks, IPNs can be divided into two groups: double networks (DN), in which both networks are held together by covalent bonds, and ionic-covalent entanglement networks (ICEN), in which one network is sacrificial and crosslinked with physical bonds [8]. Double networks are highly elastic and less sensitive to environmental effects, but their bond breakage is irreversible. Therefore, cyclic loading leads

to permanent damage of the structure, and such hydrogels are not suitable for this application. Gong et al. were the first to propose the widely used two-step method to prepare double networks. In the first step, a polymer (poly (2-acrylamido-2-methylpropane sulfonic acid) was used) was covalently crosslinked to obtain a rigid structure. The hydrogel thus obtained was immersed and swollen in a precursor solution of monomers and crosslinkers of the second network (polyacrylamide was used), which diffuses into the first hydrogel network to form a loosely crosslinked network [20]. Since this method is tedious and requires several steps, Chen et al. developed a simple one-pot method to prepare a hybrid hydrogel from agar and polyacrylamide. The obtained hydrogel had better mechanical properties, but this method proved to be more suitable for the preparation of ionic-covalent networks with one macromolecule exhibiting a sol-gel transition [21]. Ionic-covalent entanglement networks, on the other hand, are more sensitive to environmental effects and have lower mechanical stability, but they can restore ionic bonds and recover the previous properties [22]. Li et al. obtained ionically crosslinked agar entangled with a covalently crosslinked acrylic acid network coordinated with Fe3+. It proved to be a stretchable and 3D printable hybrid hydrogel with self-healing and strain-sensitive properties, which has promising properties for stretchable strain sensors able to detect human motion [23].

Nanogels

In recent years, nanomaterials have been extensively researched because they significantly affect material properties even when added in low concentrations. This is due to their high specific surface area. In addition, nanomaterials can act as reversible crosslinkers, that link multiple polymer chains together. This can improve mechanical properties, but also add functionalities such as electrical conductivity or biomedical sensing [24]. Recently, hybrid nanogels, non-fluid colloids, have been prepared as a combination of polymer networks with highly crosslinked hydrogels less than 100 nm in diameter. These materials exhibit improved elasticity and stiffness [25]. Xiao et al. prepared a block copolymer of poly (n-butyl acrylate) that exhibited amphiphilic properties and self-assembled into micelles. The particles were then mixed with poly(acrylamide) hydrogel to obtain a hybrid hydrogel whose mechanical properties could be controlled by the micelle concentration [26]. Rahali et al. used naturally derived phospholipid-based nanoliposomes to functionalize methacrylated gelatin. The resulting hydrogel exhibited increased resistance to torsion and shear and had the porous structure required for cell growth [27].

Nanoengineered ionic covalent entanglement

It has been shown that it is possible to reinforce hybrid hydrogels by combining two strategies, namely nanoreinforcement and ionic-covalent entanglement networks. This has been used to develop mechanisms that dissipate the applied force through the material and make it more tough. Chimene et al. combined GelMA for elasticity and similarity to natural ECM with ionically crosslinkable kappa-carrageenan as a more brittle component to obtain an ionic-covalent entanglement network. Nanosilicates were also added because they have permanent surface charges that allow them to form electrostatic bonds with the GelMA and kappa-carrageenan. These are weak, reversible bonds that help dissipate the force throughout material to achieve nanoreinforcement [28].

Hybrid hydrogel for dental applications

Biomaterial development is today in the scope of dentistry because there is a high demand for dental and pulp replacement and regeneration. Clinical standards for dental pulp therapy are regenerative endodontic treatment (RET)

and vital pulp therapy (VPT). The principle of VPT is direct pulp capping, in which calcium hydroxide $Ca(OH)_2$ or calcium silicates are applied directly to the pulp, forming a layer of necrotic tissue. In this way, many pulp cells are killed, which could have played a major role in tissue regeneration [29]. The evoked bleeding technique is the approach of the RET method, whose aim is to migrate stem cells into the root canals from the apical papilla. The disadvantage of this method is that the pulp is partially restored, but with changes in the healthy dental tissue [30]. The main goal of clinicians is to regenerate the pulp tissue, whereas the new tissue would be physiologically and anatomically same as healthy one without the damage to the surrounding tissue. Tissue engineering and biomaterial development have the potential to meet these requirements [1].

There are several methods for obtaining and administering scaffolds in dentistry, such as cut-to-size or injectable hydrogels, but a novel and more convenient method is to scan the damaged tissue geometry and 3D bioprint the scaffold in exact shape and size [4]. The scaffolds can be cell-laden or cell-free. Since stem cells promote regeneration, cell-laden scaffolds are the better option for this purpose. To obtain a cell-laden scaffold, it must be made of a biocompatible porous material that promotes cell adhesion but also adheres to the dental tissue [20].

Silva et al. obtained hyaluronic acid hybrid hydrogel reinforced with cellulose nanocrystals and enriched with platelet lysate as a growth factor delivery system [32]. It was shown to have pro-angiogenic activity and therefore could potentially be used for endodontic regeneration. Athirasala et al. prepared crosslinked alginate-dentin matrix hybrid hydrogels as bioinks for dental pulp regeneration. Such hydrogels were found to promote differentiation of dental pulp-like cells (OD21) [33]. Rasperini et al. reported the first human case in which a periodontal osseous defect was repaired with a 3D printed patient-specific hybrid hydrogel of PCL and hydroxyapatite in an elderly Caucasian man [34]. Similarly, Kim et al. fabricated a 3D printed hybrid hydrogel of PCL and beta-tricalcium phosphate (β-TCP) and implanted it *in vivo*. There was no evidence of inflammation and new bone formation was observed [35]. Han et al. prepared a hybrid hydrogel bioink containing fibrinogen, gelatin, hyaluronic acid, glycerol, and demineralized dentin matrix particles. High cell viability was demonstrated after 3D printing, and greater mineralization was observed with samples containing a higher amount of demineralized dentin matrix particles [36].

Future outlooks

Previous research has emphasized the importance of selecting and developing an appropriate bioink for specific purposes. Great efforts have already been made to produce a bioink with desired physical, chemical, and biological properties. Nevertheless, there is not yet a bioink that is regularly used in clinical applications. It is expected that bioinks will be used in more *in vivo* studies and clinical practice in the coming years [4].

Conclusions

Hybrid hydrogels have demonstrated many desired properties as bioinks for 3D bioprinting and tissue engineering purposes in *in vitro* and *in vivo* assessment. Despite that, clinical applications are not yet a reality. Therefore, further research is required for hybrid hydrogel-based bioinks to be regularly applied in patient treatment.

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