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Smart Materials in Regenerative Medicine

Niloufar Rezaei [1], Iman Akbarzadeh [1], Sara Kazemi [2], Leila Montazeri [2], Ibrahim Zarkesh [2], Nikoo Hossein-Khannazer[3, *], Moustapha Hassan [4], Massoud Vosough [1,4, *]

1. *Department of Regenerative Medicine, Cell Science Research Centre, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran*
2. *Department of Cell Engineering, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran 1665659911, Iran*
3. *Gastroenterology and Liver Diseases Research Center, ResearchInstitute for Gastroenterology and Liver Diseases, Shahid BeheshtiUniversity of Medical Sciences, Tehran, Iran*
4. *Experimental Cancer Medicine, Institution for Laboratory Medicine, Karolinska Institutet and Karolinska University Hospital-Huddinge, Sweden*

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ABSTRACT

Up to now, enormous smart materials have been engineered with physical stimulators such as temperature, electric field, magnetic field, light, ultrasound, mechanical stimuli, chemical stimulators such as pH and reduction, or biological stimulators such as antigen glucose and enzyme in regenerative medicine. Smart materials have numerous properties, such as responding to controlled drug release, "ON-OFF" switch activities, prolonged blood circulation, ability to specific triggers, enhanced diagnostic accuracy, increased tumor accumulation, and therapeutic efficacy. In this review, notable research achievements of smart materials responsive to various stimuli involving responsive mechanisms and applications are summarized and discussed separately.

Corresponding Information: Nikoo Hossein-khannazer, Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran; Email: *nikookhannazer@gmail.com*

Massoud Vosough, Department of Regenerative Medicine, Cell Science Research Centre, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran; Email: masvos@Royaninstitute.org

Abbreviations

AA, Acrylic acid; AC, Alternating current; APS, Ammonium persulfate; ATRP, Atom transfer radical polymerization; CA, cellulose acetate; CMC, Sodium carboxymethylcellulose; ConA, Concanavalin A; DC, Direct current; EC, Ethylcellulose; ECM, extracellular matrix; ES, electrical stimulation; FDA, Food and Drug Administration; GOx, glucose oxidase; GP, glycerol phosphate; HEC, hydroxyethylcellulose; HPC, hydroxypropylcellulose; LCST, Lower critical solution temperature; MC, methylcellulose; MNPs, magnetic nanoparticles; NIPAAM, N-isopropyl acrylamide; NSCs, neural stem cells; P(MAA-g-EG), poly (methacrylic acid-g-ethylene glycol); PAA, polyacrylic acid; PANi, polyaniline; PbAEs, poly (β-amino esters); PCL, poly(ε-caprolactone); PDAAEMA, poly (N, N-diakylamino ethylmethacrylates); PEG, poly (ethylene glycol); PEG-PCL, poly (ethylene glycol)-poly(ε-caprolactone) copolymers; PEI, poly (ethylene imine); PHPMAm, N-(2-Hydroxypropyl) Methacrylate; PL, poly(lysine); PLGA, poly (lactic/glycolic acid); pNIPAAm, poly (N-Isopropylacrylamide); PPy, polypyrrole; SNRI, serotonin-norepinephrine reuptake inhibitor; TEMED, (1,2-Bis (dimethyl amino) ethane); UCST, Upper critical solution temperature; VH, venlafaxine hydrochloride; β-TCP β-tricalcium phosphate

Introduction

Regenerative medicine, an interdisciplinary field, which combines tissue engineering and stem cell biology to generate new tissues to replace or repair damaged organs for better biological structures and functions. Since the inception of the field several decades ago, a few novel therapies, including those designed for wound healing and orthopedics applications, have been approved by Food and Drug Administration (FDA) and are now commercially available [1]. Smart or stimuli-responsive materials are an emerging class of materials used for tissue engineering and drug delivery. Today, smart materials have significant use in regenerative medicine. These materials are named "smart" because they have unique properties that enable them to respond to external variations in certain environmental conditions.

Thus, this characteristic opens up great potential in the biomedical applications since many diseases can be targeted using microenvironment stimuli. When a physical or chemical change occurs in the surrounding environment, it triggers a response by the smart materials. The response of these materials to different stimuli are generally classified into physical, chemical, and biological stimuli (Figure 1) [2]. The most common physical stimuli include temperature, electrical field, mechanical stimulation, and light. Common chemical stimuli are the pH, redox, and ionic strength. The third category is the stimulus to biological moieties include glucose concentration, different enzymes, etc. Dual responsive material systems combine two or more stimuli-responsive mechanisms in a single material [3]. In this paper, we will discuss the possible application of smart materials in regenerative medicine.

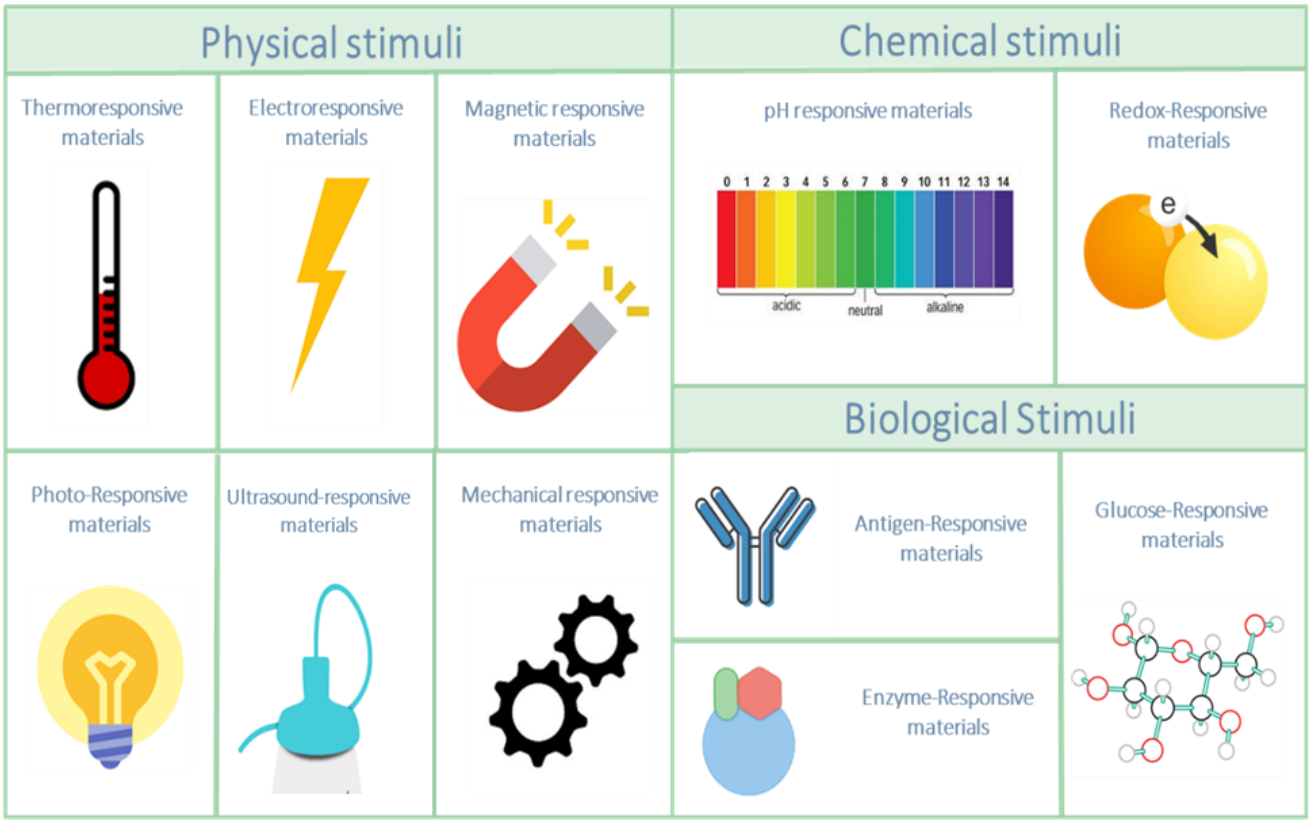

Figure 1.Classification of stimuli responsive materials by their stimuli type.

Physical stimuli

Physical stimuli mainly include temperature, electric charges, light, ultrasound, magnetic fields, and mechanical stress. These stimuli have advantages such as providing remote application and spatiotemporal control and subsequently have recently been employed widely. Also, due to the intensity of the use of these materials have to be biocompatible [4].

Thermoresponsive materials

Thermoresponsive materials change their structural properties or exhibit conformational changes in response to temperature changes. This property of polymers arises from the critical temperature of the polymer solution. At the critical temperature, the polymer solution undergoes hydrophobic and hydrophilic interactions between the polymer chains, eventually leading to the collapse or expansion of the chains. Such polymers are characterized by an upper critical solution temperature (UCST). There is only one phase above UCST, and below this temperature, the phase separation occurs. Similarly, another class of polymer solution exists that are monophasic below a specific temperature and biphasic above it. Such polymers have a lower critical solution temperature (LCST) (Figure 2). Hydrophobic groups, such as methyl, ethyl, and propyl, give temperature-sensitive properties to polymers [5].

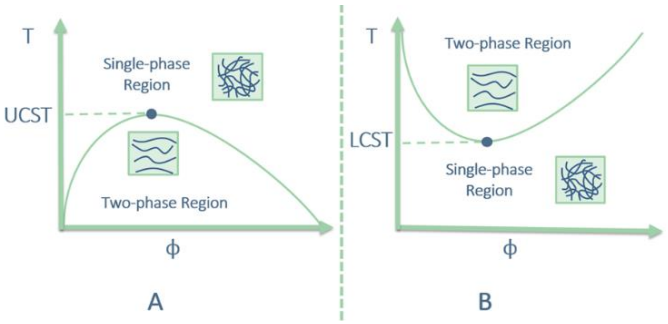

Figure 2.Temperature vs. polymer concentration. Schematic illustration of phase diagrams for polymer solution (A) UCST behaviour and (B) LCST behaviour [22].

Application of thermoresponsive materials in regenerative medicine

This chapter is a review of key thermo-responsive polymers that have been used in regenerative medicine, namely: poly (N-Isopropylacrylamide) (pNIPAAm), chitosan, cellulose and poly (ethylene glycol)-poly(ε-caprolactone) copolymers (PEG-PCL).

PNIPAAm based thermogels

PNIPAAm is a synthetic thermoresponsive polymer derived from an acrylamide monomer, N-isopropyl acrylamide (NIPAAM), consisting of amide and propyl moieties. PNIPAAm is widely used in biomedical applications as carriers for drug delivery, scaffolds for tissue engineering, and wound dressings since its LCST is close to body temperature, and its fast on-off switching. Upon cross-linking, the coil-to-globule transfer leads to a severe reduction in the volume of the pNIPAAm gel, thus quickly releases the encapsulated drug and the solvent [6]. Medicinal components can be dissolved in the solution at a lower temperature and loaded easily in the hydrogel and then increased temperature above the LCST results in gelation. For tissue engineering, we can repair damaged tissues by maintaining the normal physiological activity of cells and promoting cell proliferation and differentiation by injecting the PNIPAM solution directly into the body and triggered by the body temperature to form a 3D hydrogel. However, pNIPAAm is not used alone because of its weak mechanical properties [7]; rather, it is copolymerized with other polymers such as PEG, AA, and cellulose. If the other polymer is hydrophobic, it will decrease the LCST, and if it is hydrophilic, it will increase the LCST. PNIPAAm has been utilized with salecan, a natural, hydrophilic polysaccharide, to enhance mechanical strength and biodegradability [8]. PNIPAAm based hydrogels are weak in terms of biodegradability, resulting in problems such as the incomplete release of the drug or non-degradable scaffolds. Dextran has been introduced into PNIPAAm hydrogels through free radical polymerization to form an oral drug carrier. This delivery system also controlled the delivery of ornidazole and ciprofloxacin while demostrating good biodegradability. A study revealed that chitosan-grafted PNIPAAm as an ECM like microenvironment for stem cells enhanced cell proliferation and survival compared to pure PNIPAAm [9].

Chitosan based thermogels

Chitosan is a natural polysaccharide widely used for biomedical applications since it has good biocompatibility, low immunogenicity, and specific biological activities. Chitosan-based, in situ gelling systems, are attractive smart biomaterials used in several biomedical applications, such as drug delivery and regeneration medicine. Hybrid materials combining inorganic ceramics with organic hydrogels are highly advantageous for bone tissue regeneration because bone tissue has complex features.

Thermosensitive Thermoresponsive chitosan-based hydrogels cross-linked with β-TCP β-glycerophosphate were fabricated and reinforced via physical interactions with β-tricalcium phosphate (β-TCP) to give injectable in situ gelling bone analogs [10]. For soft tissue regeneration, injectable hydrogels are more suitable because they can be applied within any defect regardless of size or shape and provide easy and homogenous drug or cell distribution. A photo cross-linkable chitosan hydrogel was designed to encapsulate neural stem cells to facilitate the differentiation of neural stem cells (NSCs) into tubulin positive neurons and astrocytes. Thermoresponsive chitosan/ glycerol phosphate (GP) hydrogels have been used for sustained delivery of venlafaxine hydrochloride (VH), a water-soluble antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI) class. Both in vitro drug release and in vivo pharmacokinetic study via subcutaneous administration demonstrated that thermoresponsive thermosensitive chitosan/glycerol phosphate hydrogels provided better-sustained delivery of VH over 24 hours compared to VH solution [11].

Cellulose based thermogels

Cellulose is one of the most plentiful natural polymer compounds on earth, derived from plant cell walls. There are various types of cellulose derivatives, such as MC, CMC, EC, HEC, CA, HPC, and others. Moreover, cellulose and its derivatives are not toxic, making it an ideal material for regenerative medicine [12]. A "thermoresponsive" polymers should graft by copolymerization on side chains of cellulose to generate cellulose-based thermoresponsive polymers. Biocompatibility and mechanical strength of copolymers origin from cellulose components, whereas the thermoresponsive polymer grafted on the polymer backbone builds thermoresponsive behavior. The properties of synthesized copolymer depend on the polymer type, grafting density, and the degree of polymerization [13]. The copolymers of low-molecular-weight PNIPAAm and HPC backbone were synthesis via ATRP and showed long-term sustained release of macromolecular drugs at body temperature [14]. PNIPAAm was grafted to MC in different ratios using APS and TEMED as initiators, which represented the phase transition of the hydrogels reversibly within 1 min, and near body temperature [15].

PCL-PEG based thermogels

PCL is a hydrophobic, biodegradable, and biocompatible polymer. PEG due to this hydrophilic behavior has been combined with the PCL to form copolymers such as PCL-PEG. In situ gels forming systems were obtained by hybridization of PEG-PCL-based thermogels. These gels have unique properties such as high mechanical strength and high solubility [16]. Hybridization of a poly(PEG-PPGPCL-urethane) thermo-gelling system was employed to enhance the gel strength for optimizing the paclitaxel release profile in the tumor treatment. Zero-order kinetics can be seen in drug release studies [17]. In another study, Penta-block PNIPAAm-PCL-PEG-PCL-PNIPAAm thermogels were obtained by hybridization of PEG-PCL and were used for wound healing. This formulation has a three-dimensional structure with interconnected pores, which is similar to ECM. In the field of tissue engineering, this formulation can use for skin tissue engineering due to the ideal pore size for fibroblast cells, good biocompatibility for cell proliferation, and improvement of cell adhesion [18].

Electroresponsive materials

Based on the mechanism of electron conduction in ionic conductive polymers and electric conductive polymers, electroactive polymers can be classified as intrinsic and extrinsic. If the polymers contain ionic groups in their main chain and electrolytes in the medium, they are called ionic conductive polymers, and if they have high electron mobility arising from either the constitutive bonds between atoms or the presence of conductive particles, they are called intrinsic electric conductive polymers (Figure 3.A) [20].

To functionalize conductive polymers for biomedical applications, their properties, such as roughness, porosity, hydrophobicity, conductivity, and degradability should be optimized. In this regard, one route is to add monomers covalently bonded to functional molecules to increase the functionality. The optimization by this route decreases conductivity, but for biomedical applications, the biocompatibility and biodegradability of electroactive polymers should be further considered. Biomolecules or ions doped to conductive polymers to increase the biocompatibility of them [21].

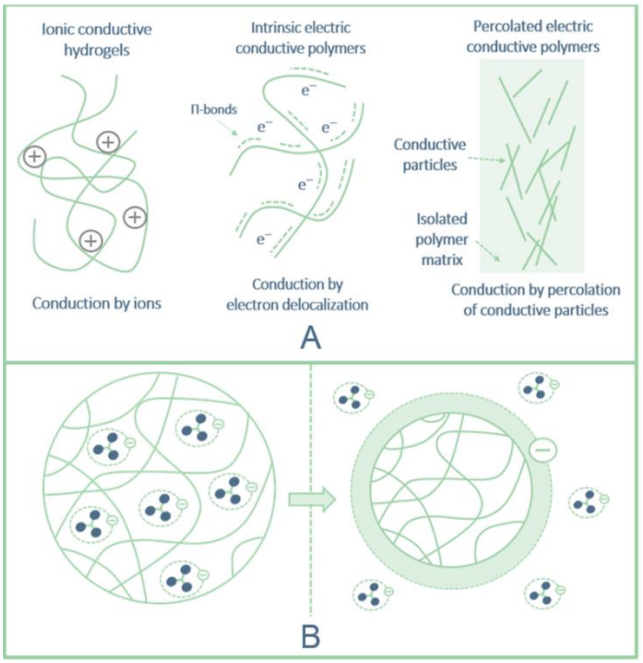

Figure 3. A) Simplified schematic diagrams showing the different conduction mechanisms of electroactive smart polymers. Ionic polymers present conductivities associated with the presence of polyelectrolytes (left side), while electric conductive polymer

Application of electroresponsive materials in regenerative medicine

Polymers for Tissue Engineering through Electrostimulation of Cells

Living cells require electric fields for several activities. For example, an electric potential difference exists across the plasma membrane, with the inside of the cell remaining more negative than the outside. The human body use electricity to maintain normal biological functions, such as signaling of the nervous system, muscle contraction, and wound healing. Electric fields are changed during major cellular events like division, development, and migration. So, several types of cells, such as fibroblasts, osteoblasts, myoblasts, chick embryo dorsal root ganglia, and neural crest cells, respond to electrical stimulation [22].

For tissue repairing, we can use ES as well as the inherent bioelectricity present in different cells. The electrical stimuli can be DC or AC [22]. The cell behavior such as orientation, proliferation, and direction of cell migration can be modified by applying electric fields as tested in corneal, epithelial, and vascular cells, among others [23,24]. Cells migrate if exposed to an electric field [25]. ES has a significant influence on nerve cells' growth and development, wound healing, and angiogenesis [26].

ES can open ion channels on cell membrane that result in deposits of ions in tissues [27]. Cellular locomotion or electrophoretic/electroosmotic are affected by altering ionic fluxes like calcium ions [25]. One of the most studied applications of electroactive polymers is the construction of scaffolds based on electrically conductive polymers for nerve tissue engineering. The scaffolds enhance the nerve regeneration process [22]. For example, for two hours' positive potential of 100 mV was passed through the PPy when seeded with PC12, and an approximately 91% increase in median neurite length was observed [28]. To enhance cell proliferation and neurite outgrowth, electric stimuli were applied to nerve cells through conductive nanofibrous scaffolds of PANi/gelatin. It resulted in better cell proliferation and neurite outgrowth compared with non-stimulated scaffolds [22].

Electroactive Polymers for Drug Delivery

Hydrogels are often used in drug delivery for two major reasons: 1) They are highly porous, making them ideal for drug loading, 2) They provide drug release rates dependent on the diffusion coefficient of the active molecule through the gel [29]. Drug release in hydrogels occurs via four main mechanisms. The first mechanism is forced convection of the drug out of the gel along with expelled water due to the electric field [30]. The second mechanism is diffusion, and the third one is the electrophoresis of charged drugs, and the fourth mechanism is drug release upon erosion of electro-erodible gels [31]. The first mechanism is based on the influence of an electric field on hydrogels. When the electric field is applied, the hydrogel deswells, solutes move out, and the drug is released [32].

Electroactive drug delivery devices can be constructed from intrinsic conductive polymers since they undergo controllable and reversible redox reactions, causing changes in polymer charge, conductivity, and volume simultaneously. These changes lead to the uptake or expulsion of charged molecules from the polymer's bulk [33]. During the oxidative polymerization process or via ion exchange through redox cycling after polymerization, anionic drugs can be loaded into the polymers, and anionic molecules can be released by an electrochemical reduction (Fig 3.B). For cationic drug release, when the neutral intrinsic conductive polymer is oxidized, the resulting net positive charge in the polymer repels the drug out of the film [34].

Magnetic responsive materials

Magnetic responsive nanomaterials and particularly MNPs have been used in various fields such as drug delivery and tissue engineering. They have a high specific surface area, chemical stability, low intraparticle diffusion rate, high loading capacity, and superparamagnetism [34]. In addition, this kind of nanoparticles are useful in biomedical fields due to their biocompatibility and long-term stability [35]. Natural magnetic polymer hydrogels are composed of the polymer matrix and magnetic inclusions, such as magnetic Fe3O4 and γ-Fe2O3 [36]. Magnetic hydrogels have unique properties, such as rapid response and remote-control ability. In drug delivery, the magnetic hydrogels are moved to the target location with the aid of the magnetic field and release drugs (Figure 4.A) [37]. The prepared magnetic hydrogels' performance depends on several parameters such as the type of hydrogel and MNPs, the concentration of gel and MNPs, and the size and distribution of MNPs in the hydrogels. The functionalized MNPs then work as a cross-linker to form a covalent coupling with polymer due to the presence of active groups. Therefore, this cross-linking process does not require additional cross-linking agents (Figure 4.B) [38]

Application of magnetic responsive materials in regenerative medicine

Recently, magnetic responsive materials have been introduced into biomedical applications. Such materials respond to the external magnetic field, giving functional structures to remotely regulate the physical, biochemical and mechanical properties of the cells' surrounding environment, tissues, or organs to improve cellular biological activity, tissues, or organs. Magnetic hydrogels can also serve as an excellent drug delivery and targeting system [39-42].

Photo-Responsive materials

Light-responsive polymers are highly advantageous for applications in regenerative medicines because light can be applied instantaneously and under specific conditions with high accuracy. The light can be applied in two main ways; it can be directly used at the polymer surface or delivered to distant locations using optical fibers [43]. The light should be minimally absorbed by cells/tissue and maximally by the polymers.

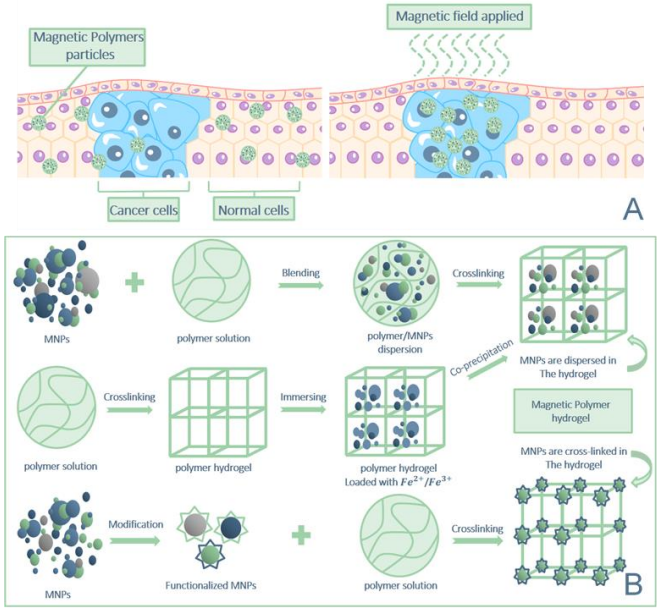

Figure 4.A) The magnetic hydrogels moved to the target location with the aid of the magnetic field and released drugs. B) three general methods for preparing magnetic hydrogels.

This happens near-infrared part of the spectrum, which is less harmful and has deeper penetration in tissues than visible light. Most photo-responsive polymers contain light-sensitive chromophores such as azobenzene [44], spiropyran [45], or nitrobenzyl groups [46] such as PAA [47], PHPMAm [48], and pNIPAAm [49].

Application of photo-responsive materials in regenerative medicine

In this section, recent progress on regenerative applications of photo-responsive materials is discussed. As photo-responsive materials are a particularly interesting options to advance drug delivery systems and tissue engineering, here we highlight their applications for photo-controlled compound releasing and cell-culturing [50].

Photo-responsive hydrogel systems are potentially useful for drug delivery systems because the release of compounds from them can be controlled by the controlling the mesh size of the network [51]. The network structure of the hydrogel matrices can be used to encapsulate macromolecules, including proteins. There is a correlation between the sizes of proteins and their diffusion coefficients in the photo-responsive hydrogel, whose mesh size can be adjusted by light [51].

Hydrogel matrices have a structure similar to hydrated living tissues and have been used as growth media for cell cultures [52]. Recently smart matrices have been generated to support, guide, and stimulate cell development [53].

Three-dimensional micro patterns can be formed inside photo-responsive hydrogels using a photolithographic technique, including two-photon excitations [54]. Moreover, the dynamic nature of photo-responsive hydrogels is beneficial because they can induce local property changes such as adhesive activity and mechanical strength, allowing for the dynamic manipulation of the environment surrounding the cells [55].

Mechanical responsive materials

In biological systems mechanical stimuli are pervasive in the form of force, pressure or deformation. Most biological tissues constantly experience various types of mechanical stimuli with the movements of the body. The differentiation of stem cells has been proved to be affected by the mechanical properties of the surrounding media [56]. Mechano-responsive hydrogels can easily adapt their physiochemical properties with the applied mechanical force/deformation. These materials are commonly found in nature [57]. Synthetic mechano-responsive hydrogels can be used as cell scaffolds, artificial muscles, therapeutic treatments, and diagnostic techniques [58]. Temperature and pH are the most commonly employed stimuli to provide a controlled release of drugs [59]. However, these methods have some challenges, such as the inability to release the drug instantaneously or the inability to stop the release reversibly. In contrast, mechanical stimulus among physical stimuli is one of the most easily accessible and universal ways for modulating the response of the systems, i.e., to trigger the release of encapsulated drugs and stop the application of stimulus immediately. The compressive mechanical stimulus is utilized to release growth factors and drugs [60]. Mechano-responsive hydrogels are classified into different categories according to the types of properties, which vary upon mechanical stimuli. In hydrogel systems, the most commonly investigated responsive properties are strain-stiffening, self-healing, shear-thinning, and mechanochromism [61].

Ultrasound-responsive materials

Another powerful remote stimulus for materials is ultrasound. Pressure waves oscillating at frequencies at or above 20 kHz can be employed for various regenerative medicine application, including controlled release from acoustically responsive carriers, acoustically triggered hydro gelation, enhancement of agent transdermal permeability via sonophoresis, in vitro manipulation of cells into defined geometric assemblies, and the temporary disruption of biological barriers to facilitate drug entry [62]. Ultrasound as a stimulus for drug delivery and tissue engineering may be used readily as an available equipment and is minimally invasive. However, there may be limitations in how deep within the tissue the ultrasound can penetrate [63].

Application of Ultrasound-responsive materials in regenerative medicine

Ultrasound-responsive materials in tissue engineering have many applications, such as manipulation of hydrogel material crosslinking to control the temporal profile of payload release. Incorporating acoustically responsive delivery particulates within a gel matrix is one strategy to fabricate ultrasound-responsive scaffold materials [62].

Several drug delivery systems use capsules or bubbles to enable acoustic responses by cavitation. Furthermore, the utilization of acoustic-responsive systems provides efficient drug release and controlled elution based upon the composition of the carriers before and after the use of high or low frequency ultrasound [63].

Chemical stimuli

Chemically dependent stimuli mainly include pH, ionic factors, and redox.

pH responsive materials

pH changes occur in many specific or pathological compartments, making it an important environmental parameter in regenerative medicine. For instance, chronic wounds have pH values between 7.4 and 5.4 [64], and tumor tissue is extracellularly acidic [65]. Therefore, unlike temperature changes, pH can be used to directly respond to a certain tissue or a cellular compartment. pH-responsive polymers must have ionizable, weakly acidic, or primary moieties attached to a hydrophobic backbone [66]. Upon ionization, a dramatic extension of coiled chains happens due to the electrostatic repulsions of the generated charges (anions or cations) (Figure 5) [67].

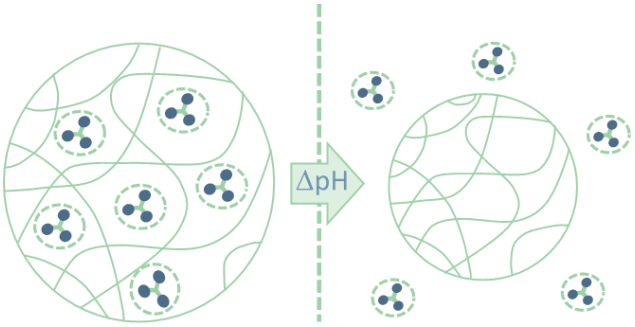

Figure 5.The swelling-shrinking behavior of pH-responsive materials or redox responsive materials makes them suitable for drug delivery and tissue engineering applications

pH responsive polymers can be in another category. These polymers exhibit protonation/deprotonation events by distributing the charge over the ionizable groups of the molecule, such as carboxyl or amino groups [68]. pH responsive polymers typically include chitosan [69], albumin [70], gelatin [71], PAA/chitosan interpenetrating polymer networks [72], P(MAA-g-EG) [73], PEI [74], PDAAEMA, and PL [75].

Application of pH-responsive materials in regenerative medicine

The swelling-shrinking behavior of pH-responsive materials in response to an external pH change makes them suitable for drug delivery and tissue engineering applications [76].

Ion-responsive materials

Polymers containing ionizable groups can be used as ion-responsive materials. The attractive Columbic interactions between oppositely charged species cause polymer systems to exhibit unusual rheological behavior. These interactions may render the polymer insoluble in deionized water but soluble in the presence of a critical concentration of electrolytes, where the attractive charge/charge interactions are shielded [77]. Therefore, polymers undergo changes in chain length, solubility, and the fluorescence quenching kinetics of chromophores bound to electrolytes when exposed to ionic strength changes [78].

Redox-Responsive materials

Polymers containing labile groups can be used to develop redox-responsive biodegradable or bioerodible systems. Acid labile moieties inside polyanhydrides [79], PLGA [80], and PbAEs [81] induce redox responsiveness. Disulfide groups are unstable in a reducing environment, and they have also been used to induce redox responsiveness [82].

Polymers with disulfide cross-links degrade when exposed to cysteine or glutathione, which are reductive amino-acid based molecules [83]. Poly (NiPAAm-co-Ru(bpy)3 can generate a chemical wave by the periodic redox change of Ru(bpy)3 into an oxidized state of the lighter color [84]. This redox reaction results in swelling and deswelling of the polymer by altering the hydrophobic and the hydrophilic properties of the polymer chains [85].

Biological Stimuli

Biologically dependent stimuli typically involve analytes and bio macromolecules such as glucose, glutathione, enzymes, receptors, and over-produced metabolites in inflammation. These materials have been used for controlled drug delivery, biosensing/diagnostics, smart films/matrices for tissue engineering, or in situ construction of structural networks [86].

Glucose-Responsive materials

Precisely engineered glucose-sensitive polymers have huge potential in the quest to generate, for example, self-regulated modes of insulin delivery. Glucose-responsive polymeric systems are typically based on enzymatic oxidation of glucose by GOx, binding glucose with ConA, or reversible covalent bond formation between glucose and boronic acids [87].

Glucose-Responsive Systems Based on Glucose-GOx

GOx oxidizes glucose to gluconic acid, resulting in a pH change in the environment. So, GOx is conjugated to the pH-sensitive polymer to yield glucose-responsive polymers [88]. The pH-sensitive polymer then exhibits a volume transition in response to the decreased pH [87]. In this way, the body's glucose level changes the polymer conformation, which, in turn, significantly affects enzyme activity and substrate access [88].

Glucose-Responsive Systems Based on ConA

Another type of glucose-responsive system utilizes the competitive binding of glucose with glycopolymer–lectin complexes. Glycopolymers tend to cross-link and/or aggregate in the presence of lectins because lectins are multivalent; however, a competitively binding saccharide can disrupt this aggregation [89]. Numerous glucose-responsive materials that are based on competitive binding between lectins and glucose have been reported. The most heavily employed lectin to impart sensitivity to glucose is ConA [90].

Glucose-Responsive Systems Based on Boronic Acid-Diol Complexation

This mechanism relies on polymers composed of only synthetic components. The boronic acids have the ability to form complexes with sugars reversibility. This ability makes them heavily employed as glucose sensors and ligand moieties during chromatography [91]. The water solubility of boronic acids can be tuned by changes in pH or diol concentration. In aqueous systems, boronic acids exist in equilibrium with their dissociated anionic form [92].

Enzyme-Responsive materials

The design of materials that undergo macroscopic property changes when triggered by enzymes' selective catalytic actions is a relatively new research area in stimuli-responsive polymeric systems. Enzymes are highly selective in their reactivity, operable under mild conditions present in vivo, and vital components in many biological pathways.

Thus, this type of sensitivity is unique. Enzyme-responsive materials are typically composed of two-part: (1) an enzyme-sensitive substrate, (2) another component that directs or controls interactions that lead to macroscopic transitions. Supramolecular architectures change, swelling/collapse of gels, or the transformation of surface properties are results of catalytic action of the enzyme on the substrate [93].

Antigen-Responsive Polymers

Antigen-antibody interactions are precise and associated with complex immune responses that help recognize and neutralize foreign infection-causing objects in the body. Antigens and antibodies can bind to each other by various noncovalent interactions, such as hydrogen bonding, van der Waals forces, and electrostatic and hydrophobic interactions. Several immunological assays for the detection and measurement of biological and non-biological substances are employed. Antigen-responsive polymers are categorized in three groups: (1) antibodies or antigens physically entrapped in hydrogel network, (2) antibodies or antigens chemically conjugated to the hydrogel network (3) or antigen-antibody pairs as reversible cross-linkers within networks [94].

Declarations

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Conflicts of interest
The authors declare no conflict of interest.

Authors' Contributions
N.R. and I.A. collected data and drafted the manuscript. S.K. and L.M. and N.H. reviewed the manuscript and checked the scientific content. I.Z. performed critical reviewing of the manuscript. M.H. and M.V. developed the concept and outlines, and confirmed the final manuscript.

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