

Review

## 내인성 조직 재생을 위한 아연 이온 방출 생체활성 하이드로젤

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(2025년 1월 30일 접수, 2025년 2월 27일 수정, 2025년 2월 27일 채택)

## Zn<sup>2+</sup>-releasing Bioactive Hydrogels for Endogenous Tissue Regeneration

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(Received January 30, 2025; Revised February 27, 2025; Accepted February 27, 2025)

**초록:** 생체활성 하이드로젤은 내인성 조직재생 향상을 위해 널리 사용되어 왔다. 이 중에서도 아연 이온 방출 생체활성 하이드로젤은 항균작용, 항염증작용, 신혈관형성, 콜라겐 합성을 증진시키는 특성을 가지고 있어 많은 주목을 받고 있다. 다양한 아연 이온 방출 생체재료들이 개발되고 있지만, 초기 빠른 이온 방출이라는 제한점을 가지고 있다. 따라서, 서방형 아연 이온 방출을 위한 다양한 개발 전략이 필요한 상황이다. 본 총설 논문에서는 내인성 조직 재생을 촉진하기 위한 생체재료 설계 전략을 다루며, 특히 아연 이온 방출 하이드로젤에 초점을 맞춘다. 아연 이온의 상처 치유 효과와 이를 활용한 생체재료의 최신 동향을 논의하며, 치료 효과를 극대화하기 위한 지속적인 이온 방출 전략을 제시한다. 이러한 통찰을 바탕으로, 본 논문은 조직 재생을 위한 차세대 생체재료 개발에 새로운 시각을 제공한다.

**Abstract:** Bioactive hydrogels are widely used in endogenous tissue regeneration. Among these, Zn<sup>2+</sup>-releasing bioactive hydrogels have attracted attention due to their antibacterial properties, anti-inflammatory responses, angiogenesis, and collagen synthesis. Although various Zn<sup>2+</sup>-releasing biomaterials have been developed, they still face limitations, such as burst ion release. Therefore, strategies for sustained Zn<sup>2+</sup> release are necessary. In this review, we highlight design strategies for biomaterials to enhance endogenous tissue regeneration, with a specific focus on Zn<sup>2+</sup>-releasing hydrogels. Our work emphasizes the therapeutic role of Zn<sup>2+</sup> in wound healing and recent advancements in Zn<sup>2+</sup>-releasing biomaterials. Additionally, we explore strategies for sustained Zn<sup>2+</sup> release to maximize therapeutic efficacy. By integrating these insights, this review offers a distinctive perspective on the development of advanced biomaterials for tissue regeneration.

**Keywords:** polymeric hydrogel, endogenous tissue regeneration, zinc ion, zinc peroxide.

### Bioactive Hydrogels for Biomedical Applications

Polymeric hydrogels are three-dimensional (3D) network structures consisting of hydrophilic polymers that can retain significant amounts of water.<sup>1,2</sup> They provide an aqueous environment with high biocompatibility and show structural similarity to the natural extracellular matrix (ECM). Owing to these unique properties, hydrogels have been extensively studied in various biomedical fields including drug delivery, wound management, and tissue regeneration.

Hydrogels can be fabricated from various polymers *via* different crosslinking mechanisms. Polymers are generally categorized into natural and synthetic polymers, whereas crosslinking mechanisms fall into two broad categories: physical and chemical reactions.

Natural polymers are derived from the biological processes of natural materials, including polysaccharides and proteins.<sup>1</sup> Examples include alginate, collagen, gelatin, chitosan, and hyaluronic acid (HA), as well as agarose and others.<sup>3</sup> These polymers offer several advantages, such as cost-effectiveness, biodegradability, and bioactive properties. However, they also come with limitations, including challenges in sterilization, low mechanical strength, and significant variability between batches.<sup>4,5</sup> In contrast, synthetic polymers are man-made materials designed for specific applications. Common examples include poly(lac-

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tic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), and polystyrene (PS).<sup>4,6,7</sup> These highly customizable polymers have adjustable mechanical and degradation properties but exhibit limited interactions with cells and the ECM.

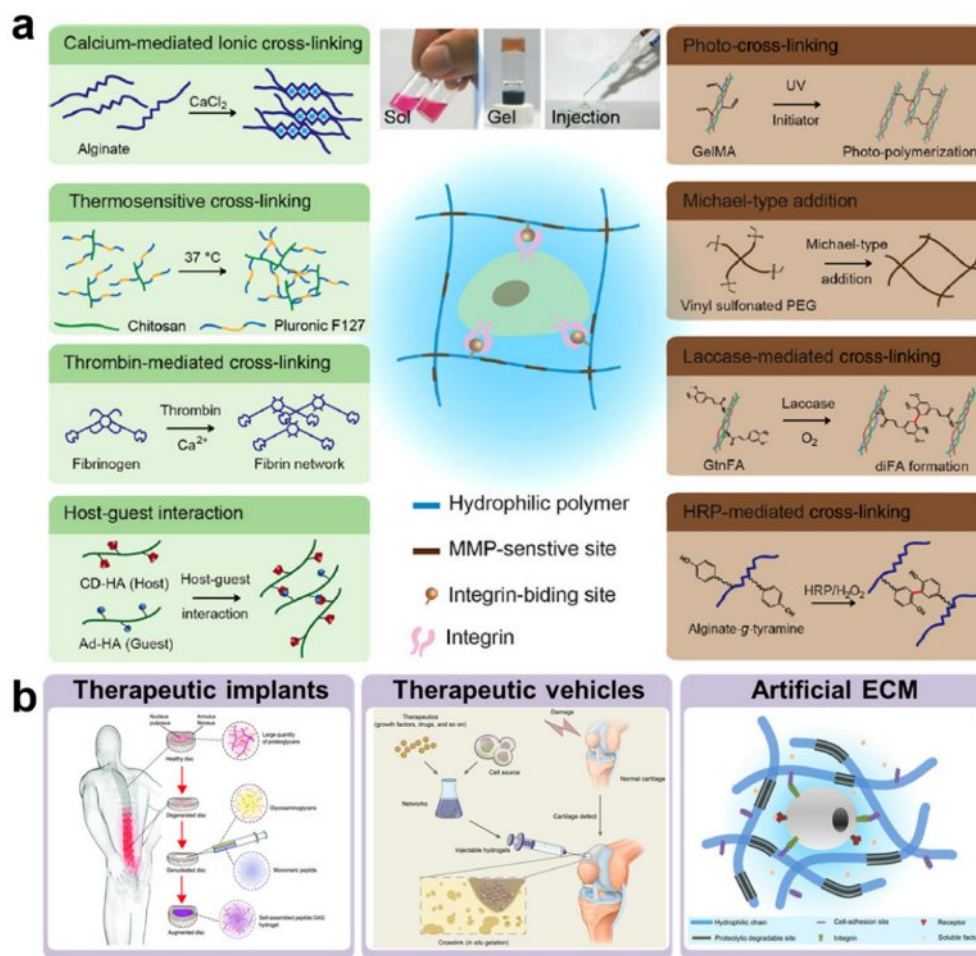
In addition to the type of polymer, the crosslinking mechanism significantly influences the properties and applications of hydrogels. Physically crosslinked hydrogels, frequently referred to as physical gels or reversible hydrogels, are created through non-covalent interactions, including ionic bonds, pH-responsive interactions, electrostatic forces, polymer entanglements, and various other methods.<sup>1,8</sup> These hydrogels are recognized for their excellent biocompatibility and their ability to respond to external stimuli, such as temperature or ion concentration. However, they often demonstrate poor mechanical stability,

especially under physiological conditions.<sup>9</sup>

Covalently crosslinked hydrogels, also known as chemical gels, are created through irreversible chemical reactions such as click chemistry, photo-crosslinking, Michael-type addition, and disulfide crosslinking. These hydrogels typically display superior mechanical stability, although they may raise biocompatibility concerns in certain applications.<sup>10,11</sup>

Polymeric hydrogels can be fabricated using various polymers and crosslinking methods. Depending on the specific application requirements, the appropriate choice of natural or synthetic polymers and the type of crosslinking methods must be carefully selected to enhance their properties and performance.

Among the various types of polymeric hydrogels, *in situ* cross-linkable hydrogels have attracted considerable attention as injectable matrices due to their sol-to-gel phase transition



**Figure 1.** Hydrogels for biomedical applications: (a) current strategies for hydrogel formation; (b) applications of *in situ* cross-linkable hydrogels in therapeutic implants, vehicles, and artificial ECM. Reproduced with permission from Refs. 10, 15–17, Park, K. M. *et al.*, *Encycl. Polym. Sci. Technol.*, **2017**, 1–16. ©2017, John Wiley & Sons, Inc. Park, S. *et al.*, *Polymers*, **2016**, 8, 23. ©2016, MDPI. Miles, D. *et al.*, *J. Mat. Chem. B*, **2016**, 4, 3225–3231. ©2016, Royal Society of Chemistry. Wu, J. *et al.*, *Theranostics*, **2020**, 10, 9843–9864. ©2020, Ivyspring International Publisher.

via various crosslinking strategies. These hydrogels can be produced using a variety of physical or chemical crosslinking reactions (Figure 1(a)).<sup>10,12</sup>

Unlike preformed hydrogels, *in situ* cross-linkable hydrogel has several advantages. They are minimally invasive to target sites, easy to handle, and capable of encapsulating bioactive molecules, such as cells, growth factors, and drugs.<sup>13,14</sup> These unique properties make *in situ* hydrogels a promising tool for various biomedical applications, including therapeutic implants, drug delivery vehicles, and artificial ECM scaffolds (Figure 1(b)).<sup>10,15,16</sup>

## Design Strategies to Engineer Biomaterials for Endogenous Tissue Regeneration

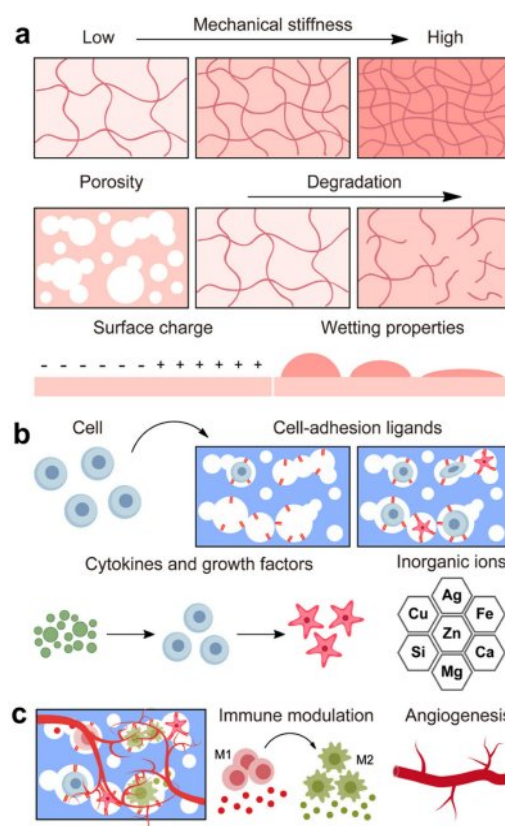
Various approaches have been explored for enhancing tissue regeneration. The traditional *ex vivo* tissue engineering method uses patient-derived cells along with biomaterial scaffolds and biological factors before being implanted into the patient's body.<sup>18</sup> However, this method has several limitations: complex cell culture processes, the need for compatible cell sources, and high costs.<sup>18</sup>

Endogenous tissue regeneration has emerged as a promising alternative for addressing these challenges. This approach modifies the microenvironment at the injury site by implanting biomaterials that facilitate host cell recruitment, self-organization, and differentiation. Compared to *ex vivo* methods, endogenous tissue regeneration offers a longer shelf life, fewer regulatory hurdles, and greater clinical applicability.<sup>19</sup>

The design strategies for bioactive materials for endogenous tissue regeneration are mainly categorized into biophysical and biochemical methods. Biophysical methods focus on the physical properties of biomaterials, including mechanical stiffness, porosity, degradation rate, and surface characteristics, which foster a microenvironment that is conducive to tissue regeneration (Figure 2(a)).<sup>2,19</sup>

For example, mechanical stiffness is crucial for angiogenesis. Matrices with moderate stiffness (800 Pa) enhanced cellular infiltration and angiogenic activity, and increased vascular endothelial growth factor receptor 2 (VEGFR2) compared to gels with either lower elasticity (700 Pa) or greater rigidity (900 kPa). In addition, porosity significantly affects blood vessel formation. Microporous scaffolds promote vascularization and tissue integration by providing an interconnected porous structure that facilitates cellular migration and tissue ingrowth.<sup>20</sup>

Biochemical methods integrate bioactive elements, such as



**Figure 2.** Design approaches for *in situ* tissue regeneration: (a) biophysical properties (e.g., mechanical stiffness, porosity, degradation, surface charge, and wettability); (b) biochemical properties (e.g., cell adhesion ligands, cytokines, growth factors, and inorganic ions); (c) endogenous tissue regeneration through biophysical and biochemical modulation.

cell adhesion ligands, drugs, genes, growth factors, and ions, to stimulate cellular activation and modulate cell behavior (Figure 2(b)). For instance, the incorporation of cell adhesion ligands can influence cell differentiation. The interaction between integrins ( $\alpha3/\alpha5\beta1$ ) and biomaterials drives human mesenchymal stem cells (MSCs) to differentiate into the osteogenic lineage, demonstrating the capacity of biomaterials to regulate cellular phenotypes.<sup>21</sup> Additionally, the incorporation of bioactive molecules plays a key role in immune modulation.<sup>22</sup> The controlled release of immunomodulatory biomolecules from biomaterials can modify the local immune microenvironment, thereby directly enhancing tissue regeneration at the application site.

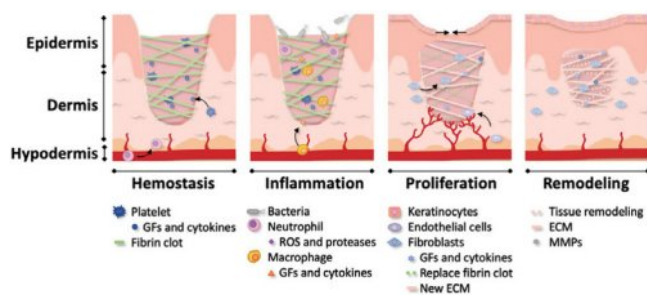
In conclusion, endogenous tissue regeneration offers a promising approach to overcoming the limitations of traditional *ex vivo* methods. By utilizing the biophysical and biochemical properties of biomaterials, this strategy can effectively modulate the microenvironment at the injury site, promoting cellular

recruitment, immune modulation, angiogenesis, and tissue remodeling (Figure 2(c)).

## Therapeutic Effects of Inorganic Ions for Skin Wound Healing

The skin is the largest organ in the body and performs various essential functions.<sup>23</sup> It protects the body from external factors, regulates temperature, and detects sensations. However, wounds can easily occur owing to external stimuli, such as mechanical stimuli, thermal injuries, or radiation exposure. When these injuries occur, the body engages in a complex healing process that consists of four overlapping phases: 1) hemostasis, 2) inflammation, 3) proliferation, and 4) remodeling (Figure 3).<sup>24</sup> The primary goal of wound healing is to restore tissue integrity effectively. Without proper treatment, these injuries may progress into chronic conditions, posing substantial obstacles to recovery. Therefore, identifying effective treatment strategies to promote tissue regeneration is critically important.<sup>2,24,25</sup>

Various inorganic ions have recently garnered significant attention in wound treatment because of their critical role in the healing process (Table 1). Silver ion ( $\text{Ag}^+$ ) is well known for its antimicrobial properties and its ability to create an anti-inflammatory environment.<sup>27,28</sup> Calcium ion ( $\text{Ca}^{2+}$ ) stimulates cell migration and proliferation, both of which are essential for tissue repair.<sup>29</sup> Additionally, copper ion ( $\text{Cu}^{2+}$ ) promotes angiogenesis and improves wound healing.<sup>30</sup> Among the reported inorganic ions,  $\text{Zn}^{2+}$  has been shown to regulate multiple stages of the wound healing process. It enhances hemostasis, exhibits antibacterial activity, immune modulation, cell proliferation, angiogenesis, supports hair follicle development, and stimulates collagen synthesis.<sup>31,32</sup> Due to these therapeutic effects,  $\text{Zn}^{2+}$  has been widely used as a therapeutic agent for wound care and tissue regeneration.<sup>23</sup>



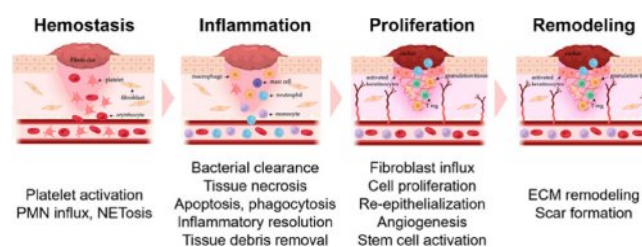
**Figure 3.** Schematic representation of the four phases of wound healing (hemostasis, inflammation, proliferation, and remodeling). Reproduced with permission from Ref. 26, Daikuara, L. *et al.*, *Adv. Funct. Mater.*, **2021**, 32. ©2021, Wiley-VCH.

**Table 1.** Various Inorganic Ions for Tissue Regeneration

Inorganic ion	Therapeutic effects	Ref.
Zinc ion ( $\text{Zn}^{2+}$ )	Antibacterial effects, Anti-inflammation, Cell proliferation, Angiogenesis, Wound closure	20, 31, 32
Silver ion ( $\text{Ag}^+$ )	Antibacterial effects, Anti-inflammation	33
Calcium ion ( $\text{Ca}^{2+}$ )	Blood coagulation, Cell proliferation, Cell migration	20
Magnesium ion ( $\text{Mg}^{2+}$ )	Cell proliferation, Cell differentiation, Cell migration	20, 31, 34
Copper ion ( $\text{Cu}^{2+}$ )	Platelet degranulation, Neovascularization, Angiogenesis	31
Iron ion ( $\text{Fe}^{2+}$ )	Inflammatory responses, Collagen maturation	31

## The Mechanisms of $\text{Zn}^{2+}$ in Wound Healing

It has been shown that  $\text{Zn}^{2+}$  plays a crucial role in the wound healing process (Figure 4).<sup>34</sup> The specific mechanisms by which  $\text{Zn}^{2+}$  contributes to wound healing are as follows. 1)  $\text{Zn}^{2+}$  penetrates bacterial cell membranes, disrupting their structural integrity and ultimately leading to cell death.<sup>35–37</sup> 2)  $\text{Zn}^{2+}$  enhances the expression of anti-inflammatory cytokines and fosters an anti-inflammatory environment at injury sites.<sup>38</sup> 3)  $\text{Zn}^{2+}$  promotes the proliferation of various cell types by regulating hormones involved in cell division, facilitating the transition from the G1 phase to the S phase of the cell cycle.<sup>39</sup> 4)  $\text{Zn}^{2+}$  enhances endothelial cell viability and proliferation by increasing the expression of vascular endothelial growth factor A (VEGFA) and platelet-derived growth factor receptor alpha (PDGFRA). Additionally,  $\text{Zn}^{2+}$  promotes cytoskeletal reorganization and F-



**Figure 4.** The therapeutic effects of  $\text{Zn}^{2+}$  on the wound healing process. Reproduced with permission from Refs. 31, 47, Lin, P. *et al.*, *Nutrients*, **2017**, 10, 16. ©2017, MDPI. Srivastave, G. *et al.*, *Polymers*, **2024**, 16, 1280. ©2024, MDPI.

actin polymerization, facilitating cell migration.<sup>40-42</sup> 5) Zn<sup>2+</sup> stimulates the migration of hair follicle stem cells near the wound.<sup>43,44</sup> 6) Zn<sup>2+</sup> enhances collagen production, essential for maintaining the mechanical strength and elasticity of skin.<sup>45</sup> Therefore, the sustained release of Zn<sup>2+</sup> can significantly improve wound healing by continuous supply of Zn<sup>2+</sup> at the injury site.<sup>46</sup>

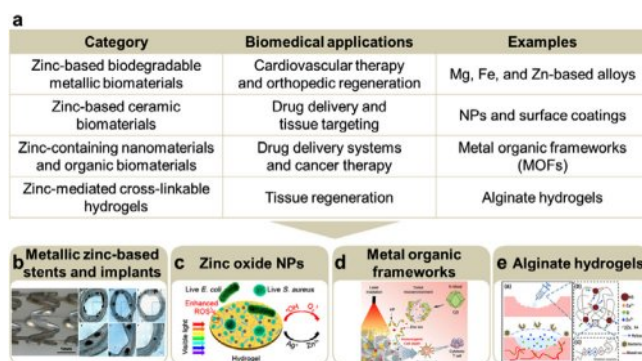
## Recent Trends in Zn<sup>2+</sup>-releasing Biomaterials

Zn<sup>2+</sup>-releasing biomaterials have been utilized in various fields including tissue regeneration and medical treatment. These materials include zinc-based degradable metallic biomaterials, zinc oxide nanoparticles (ZnO NPs), zinc-containing metal-organic frameworks (MOFs), and zinc-mediated cross-linkable hydrogels (Figure 5(a)).<sup>48</sup>

Biodegradable Zn alloys have shown promise in bone fixation and vascular stent applications due to their slow degradation rates, mechanical stability, and biocompatibility. However, pure Zn metal exhibits a low mechanical stability and a very slow degradation rate. To overcome these challenges, researchers have developed zinc alloys that offer enhanced mechanical strength and favorable degradation characteristics. In comparison to Mg and Fe alloys, zinc-based alloys degrade more slowly than Mg alloys but at a faster rate than Fe alloys (Figure 5(b)). For instance, Xiwei Liu *et al.* developed Zn–Mg–Mn alloys that demonstrate improved mechanical properties, excellent hemocompatibility, and superior mechanical stability, making them suitable for orthopedic regeneration and cardiovascular stent applications.<sup>49</sup>

ZnO NPs are extensively used in tissue regeneration due to their antibacterial and wound healing properties (Figure 5(c)).<sup>50</sup> These nanoparticles generate reactive oxygen species (ROS) and Zn<sup>2+</sup>, which penetrate bacterial membranes, disrupt their structure and interfere with DNA replication.<sup>51</sup> Furthermore, the accumulation of excess Zn<sup>2+</sup> within cells leads to cytotoxicity, causing membrane damage and apoptosis in cancer cells.<sup>52,53</sup> ZnO NPs are favored for their affordability, compatibility with biological systems, and large surface area, making them essential in many biomedical applications.<sup>50,54</sup> However, excessive production of ROS by ZnO NPs can lead to DNA damage and mitochondrial dysfunction.<sup>55</sup>

MOFs are widely utilized in drug delivery systems, cancer therapy, and bioimaging because of their high surface areas and pore volumes (Figure 5(d)).<sup>48,56,57</sup> MOFs can be used in tissue regeneration to deliver anti-inflammatory drugs. For instance, zeolitic imidazolate MOF-8 (ZIF-8), a widely studied MOF,



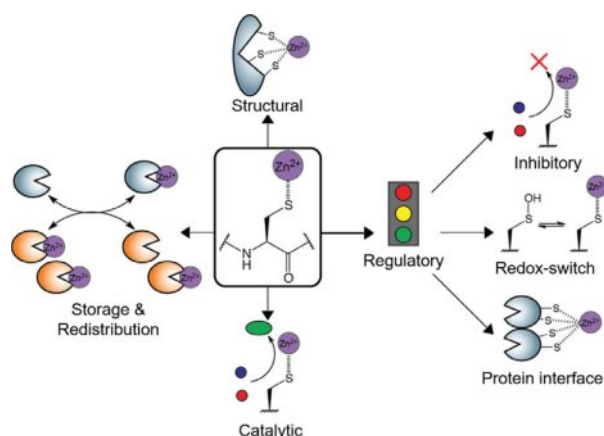
**Figure 5.** Recent trends and examples of Zn<sup>2+</sup>-releasing materials: (a) classification into biodegradable metals, ceramics, nanomaterials/organics, and Zn-based hydrogels; (b) Zn alloys for bone fixation and vascular stents; (c) nanoparticle-loaded scaffolds for antibacterial effects and wound healing; (d) Zn-based organic frameworks for cancer therapy; (e) alginate hydrogels for tissue regeneration. Reproduced with permission from Refs. 52, 60-62, Shin, H. *et al.*, *ACS Biomater. Sci. Eng.*, **2020**, 6, 3430-3439. ©2020, American Chemical Society. Li, Y. *et al.*, *ACS Appl. Mater. Interfaces*, **2017**, 9, 16054-16062. ©2017, American Chemical Society. Hehrlein, C. *et al.*, *PLoS One*, **2019**, 14. ©2019, Public Library of Science. Mao, C. *et al.*, *ACS Nano*, **2017**, 11, 9010-9021. ©2017, American Chemical Society.

has been incorporated into nanofibrous scaffolds to improve diabetic wound healing *via* sustained Zn<sup>2+</sup> release.<sup>58</sup>

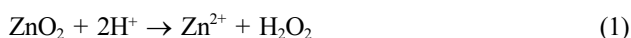
Zn<sup>2+</sup>-mediated cross-linkable hydrogels can be formed using zinc-containing ceramics, zinc chloride, and zinc sulfate.<sup>59</sup> These hydrogels enable the controlled release of Zn<sup>2+</sup> and have a wide range of potential applications in regenerative medicine (Figure 5(e)). For example, alginate hydrogels crosslinked with divalent ions such as Zn<sup>2+</sup> exhibit remarkable biocompatibility and structural similarity to the natural ECM, making them highly versatile for tissue regeneration.<sup>60</sup> Despite their promise, Zn<sup>2+</sup>-releasing biomaterials face numerous challenges, including complex fabrication processes, the need for additional additives and modification, and burst ion release that may limit their effectiveness in clinical applications.

## Zinc Peroxide-mediated Zn<sup>2+</sup>-releasing System

Zn<sup>2+</sup>-doped bioglass, Zn<sup>2+</sup>-loaded bioactive ceramics, and ZnO NPs are commonly used for Zn<sup>2+</sup> release.<sup>51,63,64</sup> However, these materials exhibit a burst release profile of Zn<sup>2+</sup>, which limits their long-term effectiveness. Therefore, zinc peroxide (ZnO<sub>2</sub>) has attracted attention as a source of sustained-release Zn<sup>2+</sup>. ZnO<sub>2</sub> decomposes and releases Zn<sup>2+</sup>, with hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) acting as an intermediate.<sup>65,66</sup> The decomposition of ZnO<sub>2</sub> proceeds *via* the following reactions:



**Figure 6.** Overview of the major functions of  $\text{Zn}^{2+}$ -cysteine complexes. Reproduced with permission from Ref. 67, Pace, N. J. *et al.*, *Biomolecules*, **2014**, 4, 419-434. ©2014, MDPI.



These reactions allow  $\text{ZnO}_2$  to release  $\text{Zn}^{2+}$  more sustainably than other  $\text{Zn}^{2+}$  delivery sources.

One of the most critical factors in the development of ion-releasing biomaterials is achieving a controlled and prolonged release of ions.  $\text{Zn}^{2+}$  has a high affinity for cysteine residues, which allows the formation of  $\text{Zn}^{2+}$ -cysteine complexes (Figure 6). Specifically, these complexes play critical roles in maintaining the structural stability of biomolecules.  $\text{Zn}^{2+}$ -cysteine complexes contribute to protein stabilization and DNA structural integrity. Zinc finger motifs, which are common domains in proteins and DNA, rely on these interactions to maintain structural integrity.  $\text{Zn}^{2+}$ -cysteine interactions regulate protein function and activity.<sup>67,68</sup> Additionally, cysteine-rich metallothioneins interact with  $\text{Zn}^{2+}$  to regulate intracellular  $\text{Zn}^{2+}$  concentration, thereby ensuring cellular homeostasis.<sup>69,70</sup> The coordination between thiol groups and  $\text{Zn}^{2+}$  ensures a regulated and sustained  $\text{Zn}^{2+}$  release over time. This mechanism enhances the performance of  $\text{Zn}^{2+}$ -releasing biomaterials and minimizes potential adverse effects. In conclusion, combining  $\text{ZnO}_2$  decomposition with the formation of a  $\text{Zn}^{2+}$ -cysteine complex presents a promising strategy for achieving controlled and sustained  $\text{Zn}^{2+}$  levels in hydrogels, paving the way for advancements in biomaterials for long-term therapeutic applications.

## Conclusions and Future Direction

This review focuses on  $\text{Zn}^{2+}$ -releasing bioactive hydrogels for endogenous tissue regeneration. Despite significant progress,

many biomaterials still face challenges with rapid ion release, which limits their long-term efficacy. Consequently, recent research has shifted toward developing strategies for sustained and controlled ion delivery, including the  $\text{ZnO}_2$ -mediated  $\text{Zn}^{2+}$  release system discussed in this article. Future studies should prioritize the development of biomaterials with prolonged ion release and multifunctional properties to enhance tissue regeneration. Additionally, a deeper understanding of the underlying biological mechanisms will be crucial for advancing biomaterial design. By integrating these strategies, researchers can pave the way for improved regenerative therapies.

**Acknowledgment:** This work was supported by the Incheon National University Research Grants in 2020 (2020-0418).

**Conflict of Interest:** The authors declare that there is no conflict of interest.

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