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Recent Advances in Dynamic Schiff Base Hydrogels for Advanced Skin Regeneration

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Abstract. Severe dermal injuries present significant clinical challenges due to delayed healing, infection, and fibrotic scarring. While hydrogels provide three-dimensional matrices that mimic the extracellular matrix (ECM), conventional statically crosslinked systems fail to replicate the dynamic viscoelasticity of native tissue. Schiff base hydrogels, crosslinked via reversible covalent imine bonds, address this limitation by exhibiting stress relaxation, shear-thinning injectability, and autonomous self-healing under physiological conditions. At the cellular level, these dynamic biophysical properties modulate integrin-mediated focal adhesion dynamics and YAP/TAZ nuclear translocation, directing stem cell spreading, migration, and lineage specification. In vivo studies demonstrate that Schiff base matrices enhance cell retention within the wound bed, promote re-epithelialization, and drive CD31/CD34-mediated neovascularization in chronic and ischemic wound models. Furthermore, tuning the hydrolysis kinetics of the dynamic imine linkages synchronizes matrix degradation with endogenous tissue ingrowth, facilitating organized collagen deposition and functional tissue restoration. Integrating dynamic covalent networks with bioactive signaling molecules provides a robust strategy for advanced skin regeneration.

Keywords: Schiff base hydrogels, Viscoelasticity, Mechanotransduction, Dermal regeneration, Dynamic covalent bonds

1. Introduction

Severe dermal damage presents an escalating clinical challenge worldwide. Unlike superficial scratches, these full-thickness wounds feature a long-term healing process, often taking months due to prolonged inflammation and bacterial interference. In modern regenerative medicine, restoring these damaged tissues relies significantly on the stem cell "niche", which is a specialized, three-dimensional microenvironment composed of extracellular matrix (ECM) components, signaling molecules, and neighboring cells [1]. The niche regulates the survival, proliferation, and differentiation of stem cells. Traditional dressings, such as cotton gauze, act merely as passive barriers, failing to synergize with this crucial niche to direct local cells.

To overcome these obstacles, advanced hydrogels have thrived as premier biomaterials. Due to their highly hydrated 3D networks, hydrogels mimic the native physical structure of the skin's ECM. They can also be packed with essential growth factors and cytokines, effectively serving as an artificial niche to shelter and guide the proliferation, migration, and targeted differentiation of stem

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cells [2]. However, while most studies focus extensively on delivering loaded bioactive cargoes (e.g., growth factors or exosomes), fewer comprehensively examine how the hydrogel's intrinsic chemical network directly regulates stem cell behavior [3]. Schiff base chemistry, a dynamic covalent linkage formed by the reversible condensation of amines and aldehydes, may provide a useful model to investigate this [4]. This review focuses on how the mechanical properties and dynamic bonding characteristics of Schiff base hydrogels regulate stem cell behavior and further mediate skin regeneration outcomes.

2. The stem cell niche and Schiff base hydrogel engineering

In human skin, resident cells, such as epidermal stem cells and hair follicle stem cells, do not function in isolation. For example, when severe deep burns destroy the superficial epidermal layer, localized niche signals are immediately activated to trigger these resident stem cells1. Upon stimulation, epidermal stem cells rapidly proliferate and migrate from wound margins to initiate re-epithelialization. Meanwhile, hair follicle stem cells residing in the deep dermis migrate upward toward the wound bed and differentiate into keratinocytes and fibroblasts, facilitating the reconstruction of functional cutaneous layers [1].

The native stem cell niche is composed of a structurally and biochemically complex ECM enriched in fibrous proteins such as collagen polysaccharides such as hyaluronic acid, as well as cell-adhesive peptides like Arg-Gly-Asp (RGD) motifs [5]. These matrix components engage integrin receptors on resident stem cells to maintain adhesion, survival, and cytoskeletal organisation5. In parallel, the niche sequesters and presents soluble signaling molecules, including vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β), which are released in spatial-temporal gradients to coordinate proliferation, migration, and differetiation [6]. These features highlight the requirement for biomaterials that not only replicate structural components of the native ECM, but also dynamically regulate both biochemical and mechanical signals within the regenerative microenvironment.

Chemically, these hydrogels are constructed via spontaneous nucleophilic addition between primary amines and active aldehydes, forming reversible imine (Schiff base) linkages under physiological conditions without toxic crosslinkers [4]. Governed by thermodynamic equilibrium, these dynamic imine bonds rapidly cleave under localized mechanical stress [4]. Upon force removal, unreacted amine and aldehyde groups at proximal sites spontaneously reassociate to re-establish covalent linkages [4]. This constant dissociation-reassociation behavior imparts macroscopically distinct self-healing properties to the dressing, allowing it to autonomously repair structural fractures and fill irregular dermal wounds, thus maintaining a continuous and protective artificial niche [4]. Among these systems, Schiff base hydrogels are particularly well suited to these requirements due to their dynamic covalent imine bonding, which enables simultaneous structural adaptability, self-healing behaviour, and tunable viscoelastic properties under physiological conditions. Despite these unique biomimetic advantages, Schiff base networks present notable limitations. The inherent reversibility and pH sensitivity of the imine bond can lead to mechanical weakness and rapid degradation in acidic chronic wounds, which challenges the long-term maintenance and structural stability of the stem cell niche [7].

3. Viscoelasticity and mechanotransduction

Native skin tissue exhibits viscoelastic rather than purely elastic behaviour, characterized by time-dependent stress relaxation in response to mechanical loading [3]. This dynamic mechanical

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property is critical for regulating how cells sense and respond to their microenvironment. In engineered biomaterials, Schiff base hydrogels provide a means to recapitulate this behaviour through reversible imine bond exchange within the polymer network, enabling continuous rearrangement of crosslinking points under physiological conditions [3].

When cells are encapsulated within these dynamic matrices, they generate traction forces through integrin-mediated focal adhesions. In contrast to permanently crosslinked systems, the reversible nature of Schiff base bonds allows local stress relaxation [3]. This mechanical adaptability is transmitted to the cytoskeleton and subsequently influences mechanotransduction pathways. One key downstream regulator of this process is the Hippo pathway effector Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) [8], which responds to cytoskeleton tension and focal adhesion dynamics by shuttling between the cytoplasm and nucleus in a context-dependent manner. Recent studies demonstrating stem cell behaviors in dynamic hydrogels show that nuclear translocation of YAP/TAZ regulates downstream gene expression associated with changes in cell morphology and fate decisions [8]. In this context, diminished physical confinement facilitates robust integrin clustering, which promotes stem cell spreading and directional migration toward the wound center to repair dermal defects [8]. In addition, the combination of tunable stiffness and rapid stress relaxation provides the exact biomimetic biophysical signaling that can bias stem cell differentiation toward skin-related lineages, such as keratinocytes or fibroblasts, ultimately supporting functional tissue regeneration [3].

A comparison with other advanced hydrogels highlights how Schiff base networks can more closely mimic the key aspects of the native stem cell niche. Traditional synthetic systems, such as photo-crosslinked GelMA, PEG hydrogels, or covalently crosslinked alginate, rely predominantly on irreversible crosslinking, resulting in relatively stable but mechanistically static networks [3]. While these materials provide excellent structural integrity and predictable mechanical properties, their limited matrix dynamics can restrict cellular remodelling of the surrounding microenvironment [3]. In such static frameworks, reduced matrix mobility may constrain cell spreading and alter cell morphology, often leading to a rounded phenotype [3]. In contrast, Schiff base hydrogels introduce dynamic covalent bonding through reversible imine linkages that exist in thermodynamic equilibrium under physiological conditions4 . Under cellular traction forces, these bonds can undergo reversible exchange reactions, enabling local network rearrangement and enhanced stress relaxation [4]. At the macroscopic level, this dynamic behaviour results in increased matrix viscoelasticity and structural adaptability, which more closely resembles native ECM remodelling. Consequently, this chemical and mechanical adaptability provides a more permissive microenvironment for cell migration and mechanosensitive signalling compared with static system [3]. However, this enhanced dynamics is balanced by reduced long-mechanical stability relative to permanently crosslinked hydrogels, highlighting an inherent trade-off between structural robustness and biological responsiveness in hydrogel design [3].

4. Schiff base hydrogels for skin tissue regeneration: current applications and research progress

Transitioning from molecular-level biophysical signaling to macroscopic therapeutic outcomes, recent studies have provided evidence that Schiff base hydrogels may enhance the functional closure of complex dermal wounds [4, 6, 7]. In various full-thickness skin defect models, these dynamically crosslinked matrices demonstrate improved capacity to support cell survival, retention, and integration within the wound microenvironment2 . Traditional rigid biomaterial scaffolds may cause cell damage via shear stress during administration. By contrast, shear-thinning imine networks

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support minimally invasive injectable delivery into irregular wound cavities and reduce mechanical perturbation of the local cell niche [4] . Once in position, the hydrogel restores its structural integrity, providing a protective barrier against bacterial infiltration while maintaining a hydrated environment conductive to wound healing and exudate management [9] .

Quantitative histological analyses reveal that wounds treated with Schiff base hydrogel dressings display a higher density of viable cells in nascent granulation tissue relative to wounds receiving passive dressing controls [2]. This increased cell retention is associated with improved re-epithelialization and more organized dermal matrix remodeling within the healing niche. The viscoelastic properties of these hydrogels may support the migration of resident hair follicle stem cells from the deeper dermis and facilitate the lateral expansion of epidermal keratinocytes from the wound edges [1]. As a result, histomorphometric studies commonly show faster wound closure within the first two weeks of application [1]. Furthermore, tissue sections typically show more continuous epidermal layers and increased granulation tissue formation compared with static scaffold systems [1] .

Ischemia remains a major barrier to healing in chronic wounds such as diabetic foot ulcers7 . Recent in vivo studies indicate that Schiff base hydrogels can facilitate angiogenic processes, leading to enhanced vascularization within the wound bed [7]. Their porous and adaptable structure allows host endothelial cells to infiltrate the matrix and participate in capillary-like network formation6. Immunofluorescence analyses using endothelial markers, such as CD31 and CD34, have shown increased vascular density within the hydrogel-treated groups [7]. This enhanced angiogenic response may improve local oxygenation and indirectly support the recruitment and activity of immune cells and endogenous regenerative populations, thereby contributing to a more pro-regenerative wound environment [7].

In the final remodeling stages of skin regeneration, the ultimate clinical goal is the restoration of functional tissue architecture rather than fibrotic scar formation. Scar tissue is clinically characterized by disorganized and densely packed collagen deposition, which can impair skin elasticity and the regeneration of appendages [10]. Schiff base hydrogels may influence this remodeling phase by regulating fibroblast activity within the resolving niche. Collagen deposition analyses confirm that Schiff base hydrogel-treated wounds often exhibit more organized collagen alignment compared with controls [10]. Moreover, the crosslinking density of Schiff base systems can be tuned to adjust degradation kinetics, allowing the material to degrade in a timeframe that more closely aligns with endogenous tissue growth [10] . As imine bonds gradually hydrolyse, the hydrogel is progressively replaced by newly deposited ECM, which may help reduce excessive fibrotic accumulation and support more organized tissue regeneration [10] .

Ultimately, to improve regenerative performance, dynamic Schiff base networks can be integrated with exogenous biological cues to optimally reconstruct the wound microenvironment. Rather than functioning solely as passive delivery vehicles, the porous and reversible nature of these hydrogels allows incorporation of bioactive niche components, such as stem-cell-derived exosomes [11]. The stress-responsive degradation of imine bonds enable sustained and localized release of encapsulated signals within the wound bed [11]. By combining mechanical adaptability with biochemical delivery, Schiff base hydrogels represent a promosing platform for supporting the repair of severe dermal defects and promoting functional tissue regeneration [11].

5. Conclusion

This review highlights the immense potential of Schiff base dynamic covalent hydrogels as biomimetic artificial niches for full-thickness skin tissue regeneration. By comprehensively

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examining the intrinsic chemical networks of these biomaterials, it was demonstrated how reversible imine bonds successfully recapitulate the dynamic viscoelasticity and stress relaxation characteristic of the native dermal extracellular matrix. This unique mechanical adaptability profoundly influences cellular mechanotransduction pathways. Specifically, it facilitates enhanced integrin clustering and subsequent YAP/TAZ nuclear translocation, which sequentially direct stem cell spreading, migration, and targeted lineage specification. Macroscopically, these dynamic biophysical advantages translate into superior therapeutic outcomes in severe wound models. The integration of shear-thinning injectability and autonomous self-healing ensures a continuous protective barrier, resulting in accelerated re-epithelialization, enhanced CD31/CD34-mediated neovascularization, and improved local cell retention. Furthermore, the tunable, synchronized degradation of the dynamic imine network perfectly accommodates endogenous tissue ingrowth, effectively minimizing abnormal fibrotic scarring and promoting the orderly functional restoration of complex skin architectures and appendages.

Primarily, the current analysis relies on a limited number of selected literature, which may not fully capture the vast spectrum of diverse Schiff base polymer formulations currently under global investigation. Additionally, this study is fundamentally a narrative synthesis and lacks original empirical research to directly validate the theoretical models discussed, particularly regarding the long-term structural stability of pH-sensitive imine bonds in highly acidic and proteolytic chronic wound microenvironments. Future research should address these specific gaps by incorporating comprehensive empirical investigations and quantitative meta-analyses to rigorously evaluate the long-term in vivo degradation profiles of these dynamic hydrogels. Furthermore, combining a broader, systematic review of the literature with standardized empirical in vivo models will enable researchers to precisely map how specific crosslinking densities quantitatively govern stem cell mechanotransduction. Advancing these empirical studies will be crucial for overcoming current mechanical limitations and accelerating the clinical translation of dynamic Schiff base hydrogels for advanced regenerative medicine.

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