International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

Mechanism-Inspired Biomaterials and Regenerative Therapies for Radiation-Induced Skin Injury

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Abstract: Radiation-induced skin injury (RISI) represents the most common complication of cancer radiotherapy, severely impairing patient health and treatment adherence. Conventional therapies show limited benefits due to the complex pathological mechanisms of RISI, creating an urgent demand for more effective approaches. Emerging biomaterials and regenerative therapies offer new opportunities for intervention. This review first outlines the key mechanisms of RISI and then highlights the mechanism-driven biomaterial design, with particular focus on the rational selection of active ingredients and advanced delivery systems. We also examine regenerative therapies such as stem cell therapy and mitochondrial transplantation, emphasizing their potential to restore function at cellular or organelle levels. Finally, the major challenges and future directions of these therapeutic strategies in RISI treatment are discussed.

Keywords: radiation-induced skin injury, biomaterials, regenerative therapies, wound healing

Introduction

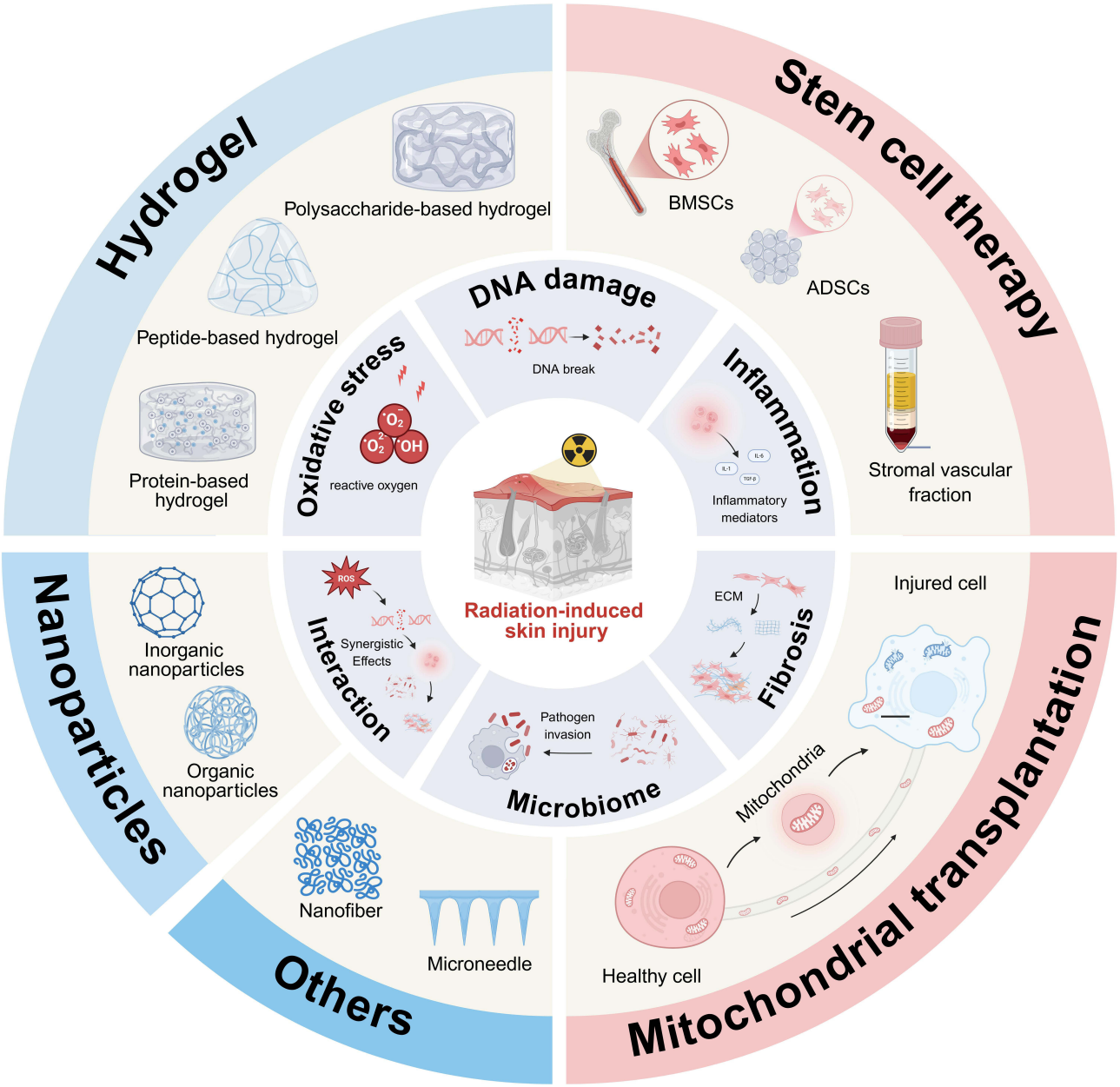
Radiation-induced skin injury (RISI) refers to pathological alterations of the skin caused by ionizing radiation, frequently observed following tumor radiotherapy and nuclear radiation exposure. The clinical manifestations include erythema, desquamation, and ulcers.[1] Approximately 95% of patients undergoing radiotherapy develop RISI, with up to 85% experiencing moderate to severe skin damage.[2] These injuries not only compromise patient health and quality of life but also diminish adherence to radiotherapy.

RISI can be classified into acute and chronic forms based on the time of onset and pathological features.[3] Acute RISI usually appears within hours or weeks following high-dose radiation exposures, presenting as erythema, swelling, and desquamation.[4] If unresolved, these acute injuries may progress to chronic RISI. Chronic RISI typically develops years later following cumulative or excessive radiation exposure, manifesting as ulceration, hyperpigmentation, and fibrosis.[5] However, the underlying mechanisms of RISI remain incompletely understood. Oxidative stress is regarded as the initial and pivotal trigger in the pathogenesis of RISI. Specifically, overproduction of radiation-induced reactive oxygen species (ROS) directly damages DNA and causes mitochondrial dysfunction, accelerating cellular damage and senescence.[6] In addition, the massive release of inflammatory mediators and infiltration of immune cells establish a sustained inflammatory environment.[7] Concurrently, defective angiogenesis and microbial imbalance further aggravate tissue damage, driving the progression of RISI.[8]

Current pharmacological treatments such as glucocorticoids, natural compounds and growth factors, as well as non-pharmacological treatments including hyperbaric oxygen therapy, low-intensity laser therapy and surgical procedures, can promote the repair of RISI to a certain extent.[9] However, there exist some limitations in clinical application, such as significant side effects, low bioavailability, and procedural complexity. Accordingly, there is an urgent need to develop novel therapeutic strategies with improved safety and efficacy. In recent years, mechanism-inspired biomaterials and regenerative therapies have shown promise for treating RISI. These biomaterials commonly combine active agents, such

https://doi.org/10.2147/IJN.S568923
Received: 19 September 2025
Accepted: 17 December 2025
Published: 8 January 2026

Graphical Abstract



as antioxidants, anti-inflammatory compounds, and angiogenic factors, with advanced delivery platforms including hydrogels, nanoparticles, nanofibers, and microneedles.[10–13] By aligning the design with the underlying disease mechanisms, these biomaterials provide efficient delivery and promote multi-target synergistic interventions. In contrast to interventions targeting pathological processes, regenerative therapies such as stem cell therapy and mitochondrial transplantation offer a strategy to address cellular dysfunction at its source.[14] Stem cells promote tissue repair and regeneration in RISI by dynamically modulating the pathological microenvironment through multidirectional differentiation, paracrine effects, and immunomodulation.[15] Mitochondrial transplantation restores cellular function and improves energy metabolism by replacing damaged mitochondria with healthy counterparts.[16] However, previous reviews mainly catalogued biomaterial types and their reported efficacy, while coverage of regenerative therapies was limited.[4,17] They

did not link the key pathological processes of RISI to the functional modules of biomaterials or regenerative strategies, thereby providing limited guidance for their further optimization.

This review offers a novel integrative overview of mechanism-inspired biomaterial designs and regenerative therapies for the treatment of RISI. It first delineates the key pathological mechanisms underlying RISI (The Mechanism of RISI), followed by an overview of current clinical treatment strategies and their limitations (Current Treatments for RISI). It then demonstrates how each mechanism is being targeted by specific biomaterial designs (Biomaterials for RISI: Active Ingredients and Advanced Delivery Systems) and regenerative approaches (Regenerative Therapies). Finally, the challenges and future prospects of these emerging therapeutic strategies are summarized (Conclusions and Future Prospects). We anticipate that this review will advance the development of biomaterials and regenerative therapies, ultimately improving the treatment of RISI.

The Mechanism of RISI

Normal wound healing typically undergoes four stages: hemostasis, inflammation, proliferation and remodeling.[18] However, this orderly repair process in RISI is disrupted. Emerging evidence indicates that the mechanism of RISI primarily involves oxidative stress, DNA damage, inflammation, fibrosis, and microbiome dysregulation (Figure 1).[19] Acute RISI is predominantly marked by oxidative stress, DNA damage, and an acute inflammatory response, whereas chronic RISI is characterized by progressive fibrosis and long-term microbiome dysregulation.[20]

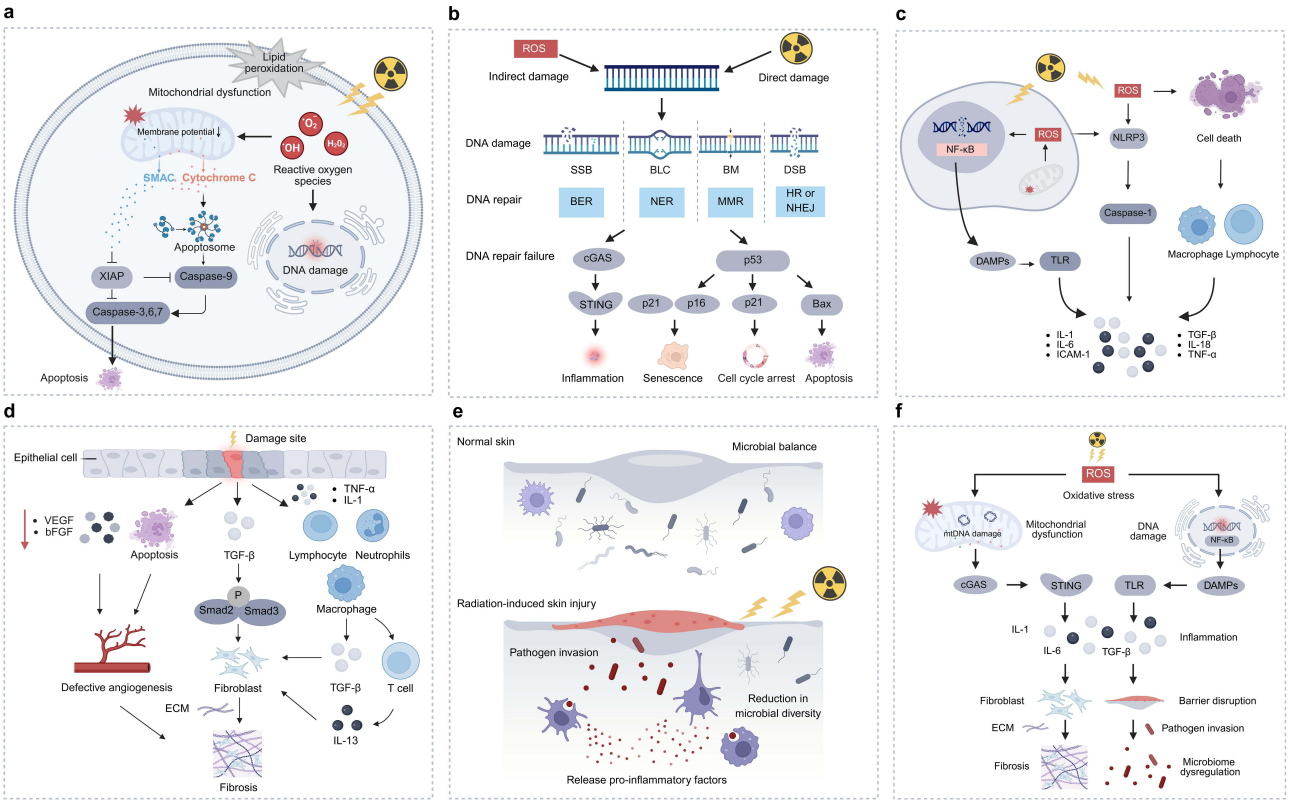


Figure 1 The mechanisms of RISI. (**a**) Oxidative stress (**b**) DNA damage (**c**) Inflammation (**d**) Defective angiogenesis and fibrosis (**e**) Microbiome dysregulation (**f**) Synergistic Effects among Mechanisms. (Created with BioRender.com).

Abbreviations: SMAC, Second mitochondria-derived activator of caspases; XIAP, X-linked inhibitor of apoptosis protein; SSB, Single-strand break; DSB, Double-strand break; BER, Base excision repair; NER, Nucleotide excision repair; MMR, Mismatch repair; HR, Homologous recombination; NHEJ, Non-homologous end joining; cGAS, Cyclic GMP-AMP synthase; STING, Stimulator of interferon genes; p53, Tumor protein p53; p21, Cyclin-dependent kinase inhibitor 1A; p16, Cyclin-dependent kinase inhibitor 2A; BAX, BCL2-associated X protein; DAMPs, Damage-associated molecular patterns; TLR, Toll-like receptor; Caspase, Cysteine-aspartic protease; NLRP3, NOD-like receptor thermal protein domain associated protein 3; IL-1, Interleukin-1; IL-6, Interleukin-6; IL-18, Interleukin-18; IL-13, Interleukin-13; ICAM-1, Intercellular adhesion molecule 1; TNF-α, Tumor necrosis factor-alpha; VEGF, Vascular endothelial growth factor; bFGF, Basic fibroblast growth factor; ECM, Extracellular matrix; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells.

https://doi.org/10.2147/IJN.S568923

Oxidative Stress

Oxidative stress is a state of imbalance in the redox system caused by the production of large amounts of ROS or the depletion of antioxidant substances,[21] which is widely recognized as the initial trigger of RISI. Ionizing radiation can induce the radiolysis of water molecules in the skin, leading to a substantial generation of ROS, including superoxide anion (O_2^-), hydroxyl radicals (·OH), hydrogen peroxide (H_2O_2), and singlet oxygen (Figure 1a). The levels of these ROS can increase approximately 2–4-fold relative to non-irradiated controls.[22] Although skin cells can mitigate ROS accumulation via the Nrf2/GCH1/BH4 signaling axis, thereby exerting antioxidant effects, radiation has been shown to suppress the expression of GTP cyclohydrolase I (GCH1) and reduce the availability of 5,6,7,8-tetrahydrobiopterin (BH4).[23] This disruption leads to endothelial nitric oxide synthase uncoupling, further exacerbating ROS production. The generated ROS can directly attack biomolecules such as DNA, proteins and lipids, leading to DNA damage, protein denaturation and cell membrane lipid peroxidation.[24] Notably, 12 hours after irradiation, nicotinamide adenine dinucleotide (NADH) dehydrogenase activity was reduced to approximately 50% of baseline, indicating the onset of mitochondrial dysfunction, which represents a hallmark event of oxidative stress-induced damage.[25] Radiation further decreases mitochondrial membrane potential and increases membrane permeability. These changes trigger the release of cytochrome c and the second mitochondria-derived activator of caspases (SMAC) from mitochondria. Cytochrome c promotes apoptosome assembly and activates the caspase cascade through Caspase-9 and downstream effector caspases, including Caspase-3, Caspase-6, and Caspase-7. At the same time, SMAC alleviates the inhibitory effect of X-linked inhibitor of apoptosis protein (XIAP) on Caspase-9, cooperating with the cytochrome c-mediated pathway to enhance apoptosis.[26] Radiation also impairs mitochondrial respiratory chain and increases electron leakage. The leaked electrons readily react with oxygen to form superoxide anions, which can subsequently be converted into other ROS, thereby amplifying oxidative stress.[27] Notably, oxidative stress not only damages the basal layer and dermis cells, leading to impaired cell proliferation and increased scaling of the skin, but also accelerates collagen degradation through activation of matrix metalloproteinases (MMPs), resulting in reduced skin elasticity and aging characteristics.[28] Moreover, oxidative stress is closely associated with inflammatory response. Excessive accumulation of ROS can upregulate the transcription of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), thereby increasing vascular endothelial permeability and exacerbating inflammatory manifestations such as erythema and swelling.[29]

DNA Damage

DNA damage induced by ionizing radiation is a critical pathogenic factor in RISI, resulting from both direct and indirect mechanisms.[30] Radiation can directly strike DNA molecule, causing destruction and shedding of bases, single strand breaks (SSB) and double strand breaks (DSB). These alterations may result in cross-linking between DNA strands or between DNA and nearby proteins.[31] Simultaneously, radiation directly disrupts the double helix structure of DNA and breaks hydrogen bonds, leading to denaturation and inactivation of DNA (Figure 1b). Indirect damage is mediated by free radicals.[32] In response to radiation-induced DNA damage, cells activate the DNA damage response (DDR) and multiple DNA repair pathways, including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ).[33] Among these pathways, SSB can be repaired by the BER pathway, whereas DSB, the most severe form of DNA damage, are only resolved via NHEJ or HR.[34] Effective DNA repair enables cells to resume the normal cell cycle and preserve their physiological functions. In contrast, when damages exceed the cellular repair threshold, the DDR shifts toward a senescence program characterized by a pronounced increase in senescence-associated β-galactosidase activity and strong upregulation of key senescence regulators, including p16 and p21. Senescent cells also secrete a wide range of senescence-associated secretory phenotype (SASP) factors such as IL-1β, IL-6, and TNF-α, which further propagate paracrine senescence and intensify tissue dysfunction, ultimately exacerbating radiation-induced skin pathology.[6,35] In addition, mitochondrial DNA (mtDNA) damage induced by ionizing radiation is sensed by cyclic GMP-AMP synthase (cGAS) in the cytoplasm. Upon recognition, cGAS catalyzes the synthesis of cyclic GMP-AMP (cGAMP), which subsequently activates the stimulator of interferon genes (STING) pathway, initiating downstream inflammatory signaling cascades and promoting a robust inflammatory response.[36,37] Furthermore, unsuccessful DNA repair can activate the tumor suppressor p53,

inducing cell cycle arrest and apoptosis, thereby impairing cellular proliferation and compromising the structural integrity and functional barrier of the skin.

Inflammation

Upon radiation exposure, skin cells rapidly secrete a variety of inflammatory factors and chemokines, including IL-1, IL-6, TNF-α, and transforming growth factor-beta (TGF-β). These mediators act on endothelial cells of local blood vessels, inducing the upregulation of adhesion molecules such as cell adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1 (VCAM1) and E-selectin.[38] It is noteworthy that the inflammatory response following radiation is dynamic and exhibits temporal changes in cytokine expression.[39] For example, IL-1 expression is markedly elevated as early as 3 hours post-irradiation, promoting leukocyte adhesion to endothelial cells.[40] IL-6 expression peaks around 6 hours after irradiation, serving as a key mediator of the acute inflammatory response.[41] By 3 weeks post-irradiation, TGF-β levels increase approximately 19-fold, driving fibroblast proliferation and contributing to tissue remodeling.[42] Moreover, ionizing radiation can directly damage biological macromolecules, activating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway and triggering cells to release a large number of damage-associated molecular patterns (DAMPs), including high mobility group protein B1 (HMGB1) and mtDNA. These DAMPs activate downstream signaling pathways in a cascade through the activation of the cellular transmembrane protein toll-like receptor 4 (TLR4), prompting the release of various inflammatory factors and accelerating the progression of inflammation.[43] In addition, the large increase of ROS caused by ionizing radiation has also become one of the triggers of inflammation. ROS activates the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome, leading to the release of caspase-1, which in turn facilitates the activation and secretion of interleukin-18 (IL-18), ultimately contributing to the inflammatory response (Figure 1c).[44] ROS can also increase the recruitment of immune cells such as neutrophils, monocytes and macrophages at the damaged site, and secrete various pro-inflammatory cytokines to form an inflammatory microenvironment. For example, M1 macrophages can release TNF-α and promote the secretion of MMPs, which disrupts the integrity of the basement membrane and compromises skin barrier damage.[45] The presence of inflammatory mediators induces vasodilatation and increased permeability, exacerbating leukocyte exudation and contributing to clinical symptoms such as redness, swelling, and stinging of the skin. In this inflammatory microenvironment, melanocytes exhibit heightened activity and produce excessive melanin to resist damage.[46] However, the melanin also results in uneven skin pigmentation and discoloration, causing undesirable appearance.

Defective Angiogenesis and Fibrosis

Defective angiogenesis is a critical pathological mechanism in RISI, intricately associated with persistent hypoxia, metabolic dysregulation, and progressive fibrosis.[47] Under physiological conditions, cutaneous injury triggers neovascularization from the existing vascular network, mediated by endothelial cell activation, proliferation, and migration. This process restores tissue perfusion and metabolic homeostasis by delivering oxygen and nutrients.[48] However, ionizing radiation directly injures dermal vascular endothelial cells, triggering apoptosis and consequently impairing angiogenic capacity.[49] In addition, radiation suppresses the expression of angiogenic factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), which significantly constrains neovascular formation. At a total radiation dose of 10 Gy, VEGF levels in rats decreased by nearly twofold, accompanied by a pronounced attenuation of angiogenesis.[50] Meanwhile, reduced bFGF expression impaired endothelial cell proliferation and decreased vascular distribution.[51] Notably, defective angiogenesis contributes to the progression of fibrosis. Radiation-induced ROS activate endothelial cells to secrete TGF-β, leading to upregulation of Smad2 and Smad3 expression and driving the transcription of fibrotic genes.[52] Meanwhile, a feedback regulatory loop exists between the TGF-β/Smad pathway and MMPs. Upregulation of TGF-β suppresses MMP activity, resulting in the accumulation of extracellular matrix (ECM), while excessive ECM deposition further promotes TGF-β activation, thereby driving progressive fibrosis.[53] Additionally, large amounts of inflammatory mediators such as TNF-α and IL-1 are released at sites of injury, activating immune cells including macrophages, neutrophils, and lymphocytes.[54] These immune cells subsequently secrete cytokines such as platelet-derived growth factor (PDGF) and TGF-β, thereby amplifying and sustaining the inflammatory response.[55] Activated macrophages release proinflammatory mediators that recruit and stimulate T cells. In turn, activated T cells

secrete interleukin-13 (IL-13), which drives fibroblasts to produce excessive collagen and fibronectin (Figure 1d).[56] This cascade results in luminal narrowing, tissue hypoxia, and impaired perfusion, ultimately culminating in endothelial fibrosis. Clinically, these pathological changes manifest as skin dryness, rigidity, and loss of elasticity.

Microbiome Dysregulation

Dysregulation of the skin microbiome represents a significant pro-inflammatory contributor in RISI. Comprising bacteria, fungi, viruses, and even Demodex mites, the skin microbiome plays a pivotal role in defending against pathogenic invasion, maintaining barrier integrity, and modulating cutaneous immune homeostasis through the bidirectional exchange of metabolites and immunoregulatory molecules.[57] For instance, colonization by skin commensal bacteria can elicit IL-17A+ CD8+ T cell responses, enhancing cutaneous innate immunity and restricting pathogen invasion.[58] In addition, the microbiota engages keratinocyte aryl hydrocarbon receptors to promote epidermal barrier differentiation.[59] However, ionizing radiation directly compromises the skin barrier, creating a permissive environment for pathogens such as Staphylococcus aureus and Pseudomonas aeruginosa to invade, adhere, and proliferate on the wound surface, thereby exacerbating infection and impairing tissue repair. An increased abundance of *Staphylococcus, Pseudomonas*, and *Nocardia* species has been associated with delayed skin recovery following radiotherapy.[60] Moreover, the coexistence of *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa* has been linked to ulcer formation in RISI. Beyond colonization, invading microorganisms further activate cutaneous immune cells to produce pro-inflammatory mediators, including IL-1α, TNF-α, and IL-1β, which in turn amplify local inflammation and aggravate wound infection (Figure 1e). Furthermore, phylum Firmicutes genera such as Lactobacillus, Streptococcaceae, and Lachnospiraceae contribute to skin wound repair.[61] However, ionizing radiation markedly diminishes skin microbiome diversity, resulting in prolonged healing of radiation-induced wounds and, in some cases, the formation of chronic ulcers.

Synergistic Effects Among Mechanisms

RISI is not driven by a single mechanism but represents a complex pathological network arising from the temporal interplay and mutual amplification of multiple factors (Figure 1f). Oxidative stress serves as the initiating event, as radiation-induced radiolysis of water rapidly elevates ROS within hours, leading to mitochondrial dysfunction, activation of the caspase cascade, and subsequent induction of apoptosis.[62] In addition, the excessive ROS generated can induce DNA damage, activate the NF-κB signaling pathway, and stimulate cells to release a broad spectrum of DAMPs, thereby promoting the robust secretion of inflammatory cytokines such as IL-1, IL-6, and TGF-β.[62] Concurrently, mtDNA damage activates the cGAS/STING pathway and its downstream inflammatory signaling cascades, further amplifying the inflammatory response.[35] The sustained inflammatory response activates immune cells to release cytokines such as PDGF and TGF-β, which stimulate fibroblasts to secrete excessive extracellular matrix, leading to vascular lumen narrowing and tissue hypoxia. Elevated TGF-β further upregulates Smad2 and Smad3 expression, accelerating fibrosis.[53] Concurrently, chronic inflammation-induced disruption of the skin barrier facilitates pathogen invasion and dysbiosis of the skin microbiota, which in turn activates resident immune cells to produce large amounts of pro-inflammatory cytokines, including IL-1 and TNF-α, thereby exacerbating inflammation and promoting wound infection.[60] Therefore, the onset and progression of RISI are fundamentally driven by a dynamic pathological network encompassing oxidative stress, DNA damage, inflammatory responses, fibrosis, and microbiome dysregulation, which collectively establish a self-amplifying vicious cycle of "damage–inflammation–impaired repair".

Current Treatments for RISI

The therapeutic strategies for RISI can be broadly categorized into pharmacological and non-pharmacological interventions. Pharmacological treatments remain the most commonly employed approaches and primarily include glucocorticoids, natural compounds, superoxide dismutase (SOD), and growth factors.[63] Glucocorticoids such as betamethasone and mometasone alleviate erythema and edema by inhibiting the release of inflammatory factors, promoting vasoconstriction and reducing leukocyte migration. For example, 0.1% mometasone furoate significantly relieved acute symptoms such as itching, burning and redness in patients with RISI in clinical studies [48]. Natural compounds, including epigallocatechin gallate (EGCG), curcumin, and calendula, as well as SOD, can reduce the incidence of radiation

dermatitis by eliminating free radicals.[64] Growth factors, such as epidermal growth factor (EGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and PDGF, accelerate wound healing by enhancing cell proliferation, migration, and angiogenesis. A clinical study has demonstrated that recombinant human epidermal growth factor reduces the area of radiation-induced dermatitis in 30.2% of patients.[65] Although pharmacological treatments represent a primary intervention for RISI, several issues remain unresolved. Prolonged use of glucocorticoids carries the risk of adverse effects such as skin atrophy and secondary infections. Natural compounds are limited by poor solubility and low bioavailability, while SOD is constrained by its inherent instability and short half-life. Growth factors are subject to individual variability and may induce hypertrophic scarring. These limitations underscore the urgent need for the development of novel and more effective therapeutic strategies.

In addition, hyperbaric oxygen therapy (HBOT), low-intensity laser therapy (LLLT), and surgery are also employed in the treatment of RISI. HBOT mitigates radiation-induced damage by enhancing tissue oxygenation and stimulating angiogenesis. Notably, one patient with refractory RISI fully recovered after 101 HBOT sessions, highlighting its potential as a conservative treatment.[66] However, its high cost and intolerance to high-pressure environments limit its widespread use. LLLT uses laser light to enhance natural wound healing by promoting mitochondrial energy conversion within cells. For instance, two patients with refractory radiation ulcers treated with thrice-weekly LLLT achieved complete wound healing within 8 weeks, with no recurrence observed during a 36-month follow-up.[67] Nevertheless, treatment efficacy depends on the dose and frequency of light exposure, and individual variability necessitates further refinement of treatment protocols. When conservative treatments fail, surgical options may be considered, though these are associated with increased difficulty and risk.

Overall, current treatments fail to comprehensively treat the complex RISI. Multifunctional interventions or approaches aimed at fundamentally replacing damaged cells are urgently needed to improve therapeutic efficacy.

Biomaterials for RISI: Active Ingredients and Advanced Delivery Systems

Biomaterials are materials that can interact with biological systems to repair or improve the function of cells and tissues. Early biomaterials used for RISI were designed to provide a physical barrier to prevent further infection of the wound. However, as insights into the pathogenesis of RISI continue to advance, single-barrier materials have proven insufficient to address its complex pathological processes. Contemporary biomaterials predominantly integrate bioactive agents such as antioxidants, anti-inflammatory compounds, and angiogenic factors with advanced delivery platforms including hydrogels, nanoparticles, nanofibers, and microneedles. These multifunctional systems not only enable efficient drug delivery and sustained release but also facilitate synergistic, multi-targeted interventions, markedly enhancing the therapeutic efficacy against RISI.

Active Ingredients

Active ingredients are functionally categorized as antioxidants, anti-inflammatory compounds, pro-angiogenic factors, and antimicrobials, corresponding to the therapeutic demands across different stages of the RISI (Table 1).[68] In acute RISI, antioxidants and anti-inflammatory agents play a critical role in early therapeutic intervention. Common antioxidant agents include SOD, vitamin E, and EGCG.[63,69] They can reduce oxidative damage and alleviate RISI by scavenging free radicals. Anti-inflammatory strategies commonly employ agents such as curcumin, resveratrol, and mometasone furoate.[36,70,71] These compounds attenuate inflammatory responses by downregulating the expression of pro-inflammatory mediators, including TNF-α and IL-6, thus alleviating erythema, edema, and pain in the affected skin.[72] Meanwhile, resveratrol has been shown to facilitate DNA damage repair via the AMPK/SIRT7/HMGB1 signaling pathway.[36]

Chronic RISI is marked by fibrosis, persistent inflammation, and non-healing ulcers. At this stage, anti-fibrotic and anti-inflammatory maintenance are essential, complemented by antimicrobial protection to prevent the development of refractory ulcers. For anti-fibrotic management, agents such as VEGF, bFGF, TGF-β inhibitors, and mesenchymal stem cell-derived exosomes can be employed to reduce collagen deposition, prevent scar formation, and mitigate skin fibrosis. For antimicrobial purposes, nanosilver or ZnO nanoparticles can be applied to inhibit infection and reduce chronic wound infection risk.[74,75]

Table 1 Pathological Features of Different Stages of RISI and Representative Active Ingredients, Their Functions, and Mechanisms for Therapeutic Intervention

Stage	Clinical Manifestation	Pathological Features	Key Molecular Biomarkers	Representative Active Ingredients	Function	Mechanism	Reference
Acute RISI	Erythema, swelling, dry or moist desquamation	Oxidative stress	ROS	SOD, EGCG, Vitamin E	Antioxidative	Eliminate ROS to reduce oxidative damage to cells	[63,69,73]
		DNA damage	γH2AX	Resveratrol	Promoting DNA repair	Promote DNA repair through the AMPK/SIRT7/HMGB1 pathway	[36]
		Inflammation	TNF-α, IL-1β, IL-6	Curcumin, Resveratrol, Mometasone Furoate	Anti-inflammatory	Reduce the expression of inflammatory mediators such as TNF-α and IL-6	[36,70,71]
Chronic RISI	Ulceration, hyperpigmentation, and fibrosis	Fibrosis	TGF-β / Smad, α-SMA, Collagen I	VEGF, bFGF, TGF-β inhibitors	Anti-fibrosis	Activate the PI3K/Akt pathway to promote angiogenesis while inhibiting TGF-β/Smad signaling to prevent scar formation	[74,75]
		Microbiome dysregulation	β-diversity	Nanosilver or ZnO nanoparticles	Antimicrobial	Inhibit bacterial growth to reduce chronic wound infection risk	[76]

Abbreviations: ROS, reactive oxygen species; SOD, superoxide dismutase; γH2AX, Phosphorylated H2A histone family member X; EGCG, epigallocatechin gallate; AMPK, AMP-activated protein kinase; SIRT7, sirtuin 7; HMGB1, high mobility group box 1; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; IL-6, interleukin-6; α-SMA, α-Smooth Muscle Actin; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; TGF-β, transforming growth factor-beta.

Active ingredients should therefore be selected rationally according to the pathological features of different stages of RISI. Moreover, integrating these agents with advanced delivery systems tailored to their physicochemical properties enables more precise interventions.

Advanced Delivery Systems

Although numerous active agents have shown promising therapeutic potential for RISI, their clinical application remains constrained by inherent limitations such as low solubility, poor stability, and short half-lives. The development of delivery systems is therefore pivotal for the rational design of functional biomaterials. An effective delivery platform not only enhances the physicochemical properties of active ingredients but also ensures targeted and sustained release at the lesion site, thereby substantially improving therapeutic efficacy. In the following section, we outline representative delivery platforms for RISI, including hydrogels, nanoparticles, nanofibers and microneedles, with emphasis on their unique features and design strategies for functional biomaterial development, and summarize the composition, physicochemical properties, drug release behavior, and therapeutic outcomes of various biomaterials (Table 2).

Hydrogels

Hydrogels, one of the most widely utilized biomaterials for the treatment of RISI, have a hydrophilic crosslinked network structure that enables them to function as wound dressings to absorb exudate and maintain a moist microenvironment.[82] Additionally, the tunable swelling and degradation characteristics of hydrogels make them ideal carriers for the controlled and sustained release of therapeutic agents. Hydrogels can be prepared from a variety of materials, including natural substances (polysaccharides, peptides, and proteins) as well as synthetic polymers.[83] In RISI, hydrogels are mainly prepared from natural

Table 2 Composition, Physicochemical Properties, Drug Release Behavior, and Therapeutic Outcomes of Various Biomaterials

Delivery System	Representative Materials	Composition	Physicochemical Parameters			Drug Release Behavior	Therapeutic Efficacy	Reference
			Swelling Ratio	Mechanical Modulus	Degradation Rate			
Hydrogels	CSGA/ODex	Gallic acid-modified chitosan and oxidized dextran	15%-35%	G′>G″	50% degradation after 7 days	/	Wound closure rate approaches 40% by day 7	[77]
	PHF@Res	HAMA, Pluronic F127 diacrylate, Prussian blue nanoparticles and resveratrol	80%	G'>G"	20%-70% degradation after 7 days	The cumulative release rate in the first 12 hours can reach 25.52±2.78%	Restored to a state comparable to normal skin on days 14 and 21	[78]
	AHPE hydrogel	HAMA, acrylamide, a disulfide-containing hyperbranched poly(β-acylhydrazide) macromolecule, and epidermal growth factor	175%	G'>G"	/	The growth factor release rate after 12 hours of X-ray irradiation treatment of the gel was 64.15%.	Wound repair was observed around day 14	[10]
	AHP-Cur/EGCG	Alginate, hyaluronic acid, poly-L-lysine, curcumin, and EGCG	/	Compressive modulus: 0.0225–0.0518 MPa	/	95.2 ± 1.8% of EGCG and 46.1 ± 2.9% of curcumin were released within 48 hours	The epidermis and hair follicles recovered well by day 14	[71]
	GK@TA^{gel}	$K_2(SL)_6K_2$ (KK) peptide, glucomannan, and tannic acid	Below 150%	G′>G″	90.3% degradation after 14 days	/	Erythema disappeared by day 21	[79]
	Cur@TA-Gel	GelMA, curcumin, and tannic acid	/	/	The remaining weight ratio on day 25 was 30.93%	Nearly 70% was released within 72 hours	The wound showed significant healing and was covered with hair by day 21	[80]
Nanoparticles	PC@CuS	Phycocyanin, Cu^{2}+ and S^{2-}	/	/	/	65% of PC and CuS was released after 8 hours	The wound achieved complete closure by day 25	[11]
	VEGF-CS	Chitosan nanoparticles loaded with VEGF	/	/	/	VEGF release was 10–20% within the first two days and reached up to 90% by day 30	Microvessel density increased significantly	[81]
Microneedles	SF+MNs+DFO	Silk fibroin, acrylamide and desferrioxamine	Up to 80%	0.20 N/needle	/	Approximately 50% of the drug was released within the first 24 hours	Wound healing rate exceeded 90% by day 10	[13]

Abbreviations: G', storage modulus; G", loss modulus; VEGF, vascular endothelial growth factor; EGCG, epigallocatechin gallate; HAMA, methacrylated hyaluronic acid; /, not mentioned in the study.

https://doi.org/10.2147/IJN.S568923

materials and enhanced by modification, whereas the use of synthetic polymers remains comparatively limited. Figure 2 provides a systematic overview of the design and function of hydrogels based on natural materials.

Polysaccharide-Based Hydrogels

Polysaccharides are macromolecular compounds composed of monosaccharide units linked by glycosidic bonds, exhibiting excellent biocompatibility, biodegradability, and low immunogenicity. The common types of polysaccharide include chitosan, hyaluronic acid, alginate and cellulose.[84]

Chitosan is the only natural polysaccharide that can form a cationic state. Under physiological conditions, a large amount of $-NH_2$ on the molecular chain of chitosan is protonated and converted into positively charged $-NH_3^+$, which can easily bind to negatively charged components such as platelets and bacterial cell walls, exerting hemostatic and antibacterial effects.[85] In Addition, a variety of functional groups in the structure of chitosan can be modified. For instance, chitosan reacts with the quaternary ammonium reagent, 2, 3-epoxy-propyl trimethyl ammonium chloride, to produce quaternary aminated chitosan, which exhibits higher positive charge density and enhanced antibacterial properties.[86] Peng et al developed an injectable hydrogel composed of quaternized chitosan, oxidized sodium alginate, and mesenchymal stem cell-derived exosomes (HACC/OSA@Exos) (Figure 3a), which demonstrated potent antibacterial activity, achieving inhibition rates of up to 99% against *Escherichia coli* and *Staphylococcus aureus*. Additionally, the treatment group displayed markedly increased CD31 and CD34 positive microvascular density, indicating a pronounced pro-angiogenic effect.[87] Gallic acid can be grafted onto chitosan to impart free radicals scavenging capability via a coupling reaction mediated by N-hydroxysuccinimide (NHS) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). The combination of gallic acid-modified chitosan (GSGA) and oxidized dextran (ODex) forms an aqueous hydrogel (CSGA/ODex) that exhibits enhanced antioxidant capacity with increasing GSGA content and effectively promotes wound healing in a model of combined radiation and burn injuries.[77]

Hyaluronic acid (HA), a linear polyanionic polysaccharide, is a major constituent of the extracellular matrix. Its molecular structure, abundant in carboxyl and hydroxyl functional groups, facilitates extensive hydrogen bonding with water molecules, thereby conferring remarkable water retention capacity similar to that of a sponge.[88] Additionally, the

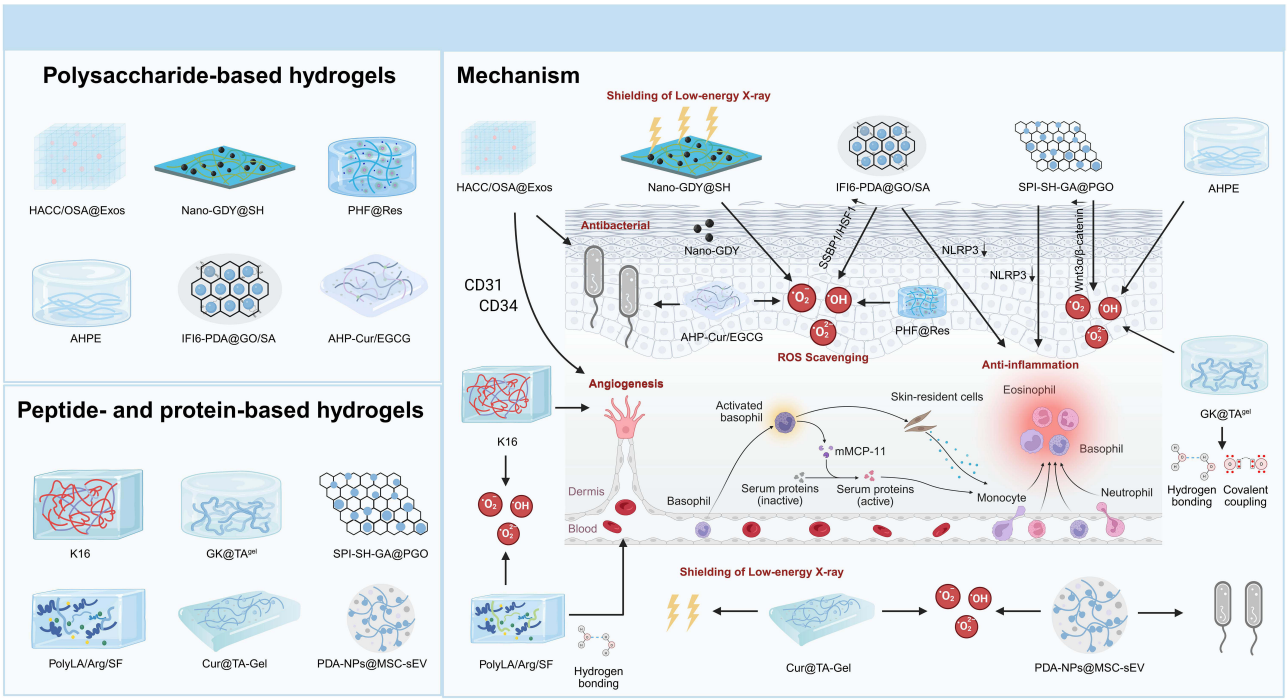


Figure 2 The design and function of hydrogels for the treatment of RISI. (Created with https:BioRender.com).
Abbreviations: NLRP3, NOD-like receptor thermal protein domain associated protein 3; SSBP1, Single-stranded DNA-binding protein 1; HSF1, Heat shock factor 1; Wnt3α, Wingless-type MMTV integration site family member 3 alpha; β-catenin, Beta-catenin; mMCP-11, Mouse mast cell protease 11.

carboxyl groups in HA can coordinate with metal ions to form crosslinked hydrogels with favorable viscoelastic properties, making HA-based hydrogels widely applicable in wound healing.[89] Sodium hyaluronate hydrogel serves as a physical barrier to reduce the damage of low-energy X-rays. When incorporated with nano-graphyne (Nano-GDY @SH), which possesses potent free radical scavenging capacity, the system confers dual radioprotective effects.[90] However, hyaluronic acid exhibits limitations such as a single biological function and an uncontrollable degradation rate, which need to be optimized by chemical modification. Methacrylated hyaluronic acid (HAMA) is generated by the reaction of methacrylate with hyaluronic acid, which has good biodegradability, high water-absorption, and light-curing properties.[91] Shen et al developed an in situ curable dual-network hydrogel by combining HAMA with Pluronic F127 diacrylate. Polyvinylpyrrolidone (PVP)-modified Prussian blue nanoparticles and resveratrol were incorporated to formulate the PHF@Res hydrogel (Figure 3b), which exhibited both antioxidant and anti-inflammatory properties.[78] This multifunctional hydrogel significantly enhanced epithelial regeneration and angiogenesis, thereby accelerating the healing of RISI. Responsive functional groups can be further introduced through material design to achieve effects such as controlled drug release. For instance, Xia et al developed an X-ray-responsive AHPE hydrogel by introducing disulfide bonds (Figure 3c).[10]

Alginate is a natural anionic polysaccharide, characterized by carboxyl groups in its molecular structure, which can form cross-links with metal ions to generate hydrogels. These hydrogels typically exhibit high hydrophilicity and excellent biocompatibility.[92] Hao et al developed a composite hydrogel composed of polydopamine conjugated to sodium alginate and graphene oxide for the modification of interferon-α-inducible protein 6 (IFI6-PDA@GO/SA). This hydrogel markedly reduced ROS levels and suppressed NLRP3 inflammasome activation. Compared to the 44-day wound healing period observed in the irradiated control group, treatment with this hydrogel reduced the healing time to 26 days in mice, which may be attributed to the activation of the SSBP1/HSF1 signaling pathway.[93] However, the high moisturizing property of hydrogels also make them susceptible to bacterial adhesion. To overcome this limitation, Zhang et al developed a neutrally charged alginate-based hydrogel (AHP-Cur/EGCG) by balancing negatively charged alginate with positively charged polylysine. The resulting hydrogel exhibited pronounced anti-biofouling performance, with a bacterial adhesion rate approaching 0%. Meanwhile, incorporation of curcumin and EGCG into the hydrogel provides antioxidant and anti-inflammatory properties that significantly mitigate RISI.[71]

Peptide and Protein-Based Hydrogels

Peptide-based hydrogels are typically formed through the self-assembly of short peptide chains, driven by non-covalent interactions such as hydrogen bonding, hydrophobic forces, and π-π stacking.[94] These peptides closely mimic endogenous human peptides, conferring excellent biocompatibility with low immunogenicity and safe degradability.[95] Furthermore, with advances in precise amino acid sequence engineering, peptide hydrogels can be functionally customized and engineered to be stimuli-responsive. For example, Hao et al developed an antioxidant heparin-mimetic peptide hydrogel (K16, KYKYEYEYAGEGDSS-4Sa), in which the sequence KYKYEYEY was modified by substituting tyrosine (Y) for phenylalanine (F), endowing the hydrogel with the ability to scavenge ROS. The AGEGDSS-4Sa segment is a heparin-mimetic peptide with pro-angiogenic and anti-inflammatory properties. The combination of these two peptides results in a hydrogel that accelerates complete healing of RISI within 21 days (Figure 4a).[96] It is worth noting that glycopeptides composed of peptides and polysaccharides are the key functional units of extracellular matrix, which has gradually become an important exploration direction of biomimetic repair materials. Feng et al developed an ECM-mimetic glycopeptide hydrogel (GK@TA^{gel}) consisting of K2(SL)6K2 (KK) peptides, dextromannan and tannic acid. The presence of TA enhanced the adhesion of hydrogels to biological substrates through multiple interactions, including hydrogen bonding, coordination bonding, cation–π and π–π interactions, and covalent coupling. As a result, GK@TA^{gel} effectively promoted macrophage polarization, with M2 macrophages reaching 60% by day 21, and eliminated more than 90% of total H_2O_2. (Figure 4b).[79] However, the mechanical strength of polypeptide-based hydrogels is generally limited, which may restrict their applicability in environments with high mechanical demands, necessitating the use of alternative strategies such as the integration of composite nanomaterials to improve their performance.

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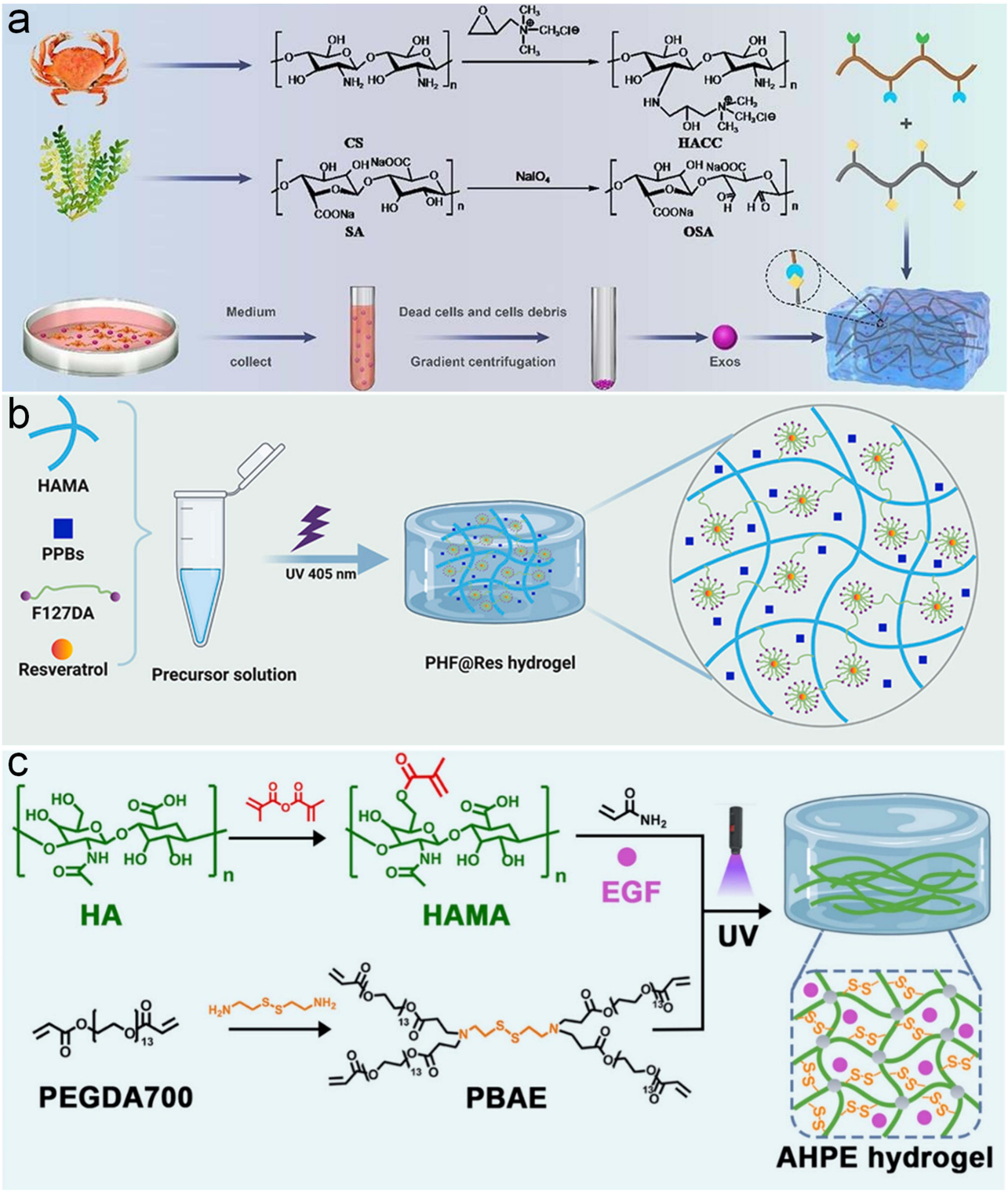

Figure 3 Specific preparation of polysaccharide-based hydrogels. (**a**) HACC/OSA@Exos hydrogel.[87] Copyright 2024, Elsevier B.V. (**b**) PHF@Res hydrogel.[78] Copyright 2025, Elsevier B.V. (**c**) AHPE hydrogel.[10] Copyright 2025, American Chemical Society.

Abbreviations: CS, Chitosan; HACC, Hydroxypropyltrimethyl ammonium chloride chitosan; SA, Sodium alginate; OSA, Oxidized sodium alginate; Exos, exosomes; HAMA, Methacrylated hyaluronic acid; PPBs, Pluronic polymeric nanoparticles; F127DA, Pluronic F127 diacrylate; PEGDA700, Poly(ethylene glycol) diacrylate 700; PBAE, Poly(beta-amino ester); EGF, Epidermal growth factor.

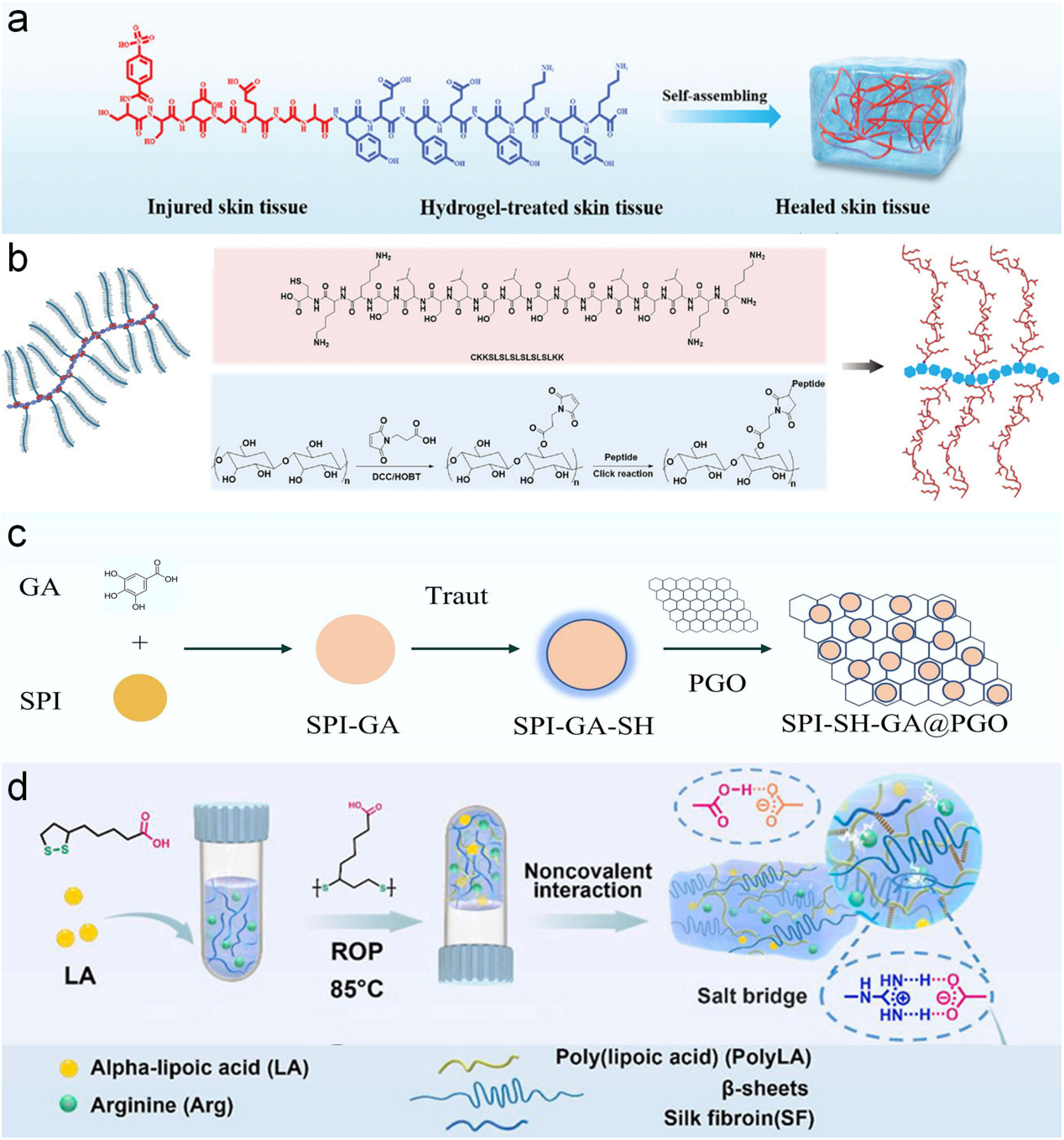

Figure 4 Specific preparation of peptide and protein-based hydrogels. (**a**) K16 peptide hydrogel.[96] Copyright 2023, Wiley. (**b**) GK@TA^{gel}.[79] Copyright 2023, Wiley. (**c**) SPI-SH-GA@PGO hydrogel.[97] Copyright 2023, Elsevier B.V. (**d**) PolyLA/Arg/SF hydrogel.[98] Copyright 2024, Elsevier B.V.
Abbreviations: GA, Glutaraldehyde; SPI, Soy protein isolate; PGO, Porous graphene oxide; LA, Lipoic acid; ROP, Ring-opening polymerization.

Protein-based hydrogels are three-dimensional network materials formed from natural or recombinant proteins by physical or chemical cross-linking, with excellent biocompatibility, adjustable mechanical strength, and highly bionic extracellular matrix properties.[99] Vegetable proteins, collagen, silk proteins, gelatin are common materials.

Soy protein, one of the most widely used plant proteins, can be induced to form stable gels through thermal processing, acidification, or enzymatic crosslinking, and exhibits excellent mechanical strength and bioadhesive properties.[100] Zhou et al developed a graphene oxide–hybrid soy protein-based hydrogel (SPI-SH-GA@PGO)

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(Figure 4c), which accelerated the healing of radiation-induced skin injury by activating the Wnt3α/β-catenin signaling pathway, thereby alleviating oxidative stress and NLRP3 inflammasome activation, and reduced the wound closure time from over 40 days to 25 days.[97]

Fibroin is a natural fibrous protein with abundant binding sites. Under the induction of external factors such as pH, ultrasound and surfactant, the secondary structure of fibroin can be transformed from random curling to β-folding, which promotes cross-linking between molecular chains and enhances the intermolecular forces as well as hydrogel strength.[101] Zhang et al skillfully combined arginine, α-lipoic acid, and fibroin to construct a multifunctional hydrogel (PolyLA/Arg/SF) without introducing other unnatural molecules, which exhibited efficient ROS scavenging, pro-angiogenic, and wet-tissue adhesion abilities for adjuvant treatment of RISI (Figure 4d).[98]

Gelatin, a hydrolyzed collagen derivative rich in amino and carboxyl groups, exhibits excellent biocompatibility and low immunogenicity.[102] However, gelatin dissolves at high temperatures and forms gels at low temperatures, resulting in hydrogels with limited thermal stability and poor mechanical strength. To overcome these limitations, gelatin can be functionalized through reaction with methacrylamide to produce gelatin methacryloyl (GelMA), which exhibits enhanced stability and improved mechanical properties.[103] Huang et al used GelMA to deliver nanoparticles assembled with curcumin and tannic acid (Cur@TA-Gel), which realized the dual functions of physical absorption and chemical scavenging of ROS for the effective treatment of radiation dermatitis.[80] Furthermore, Fang et al prepared an injectable, viscous, and self-healing hydrogel (PDA-NPs@MSC-sEV) using carbamide hydrazide-modified gelatin and oxidized hyaluronic acid, incorporating polydopamine nanoparticles and mesenchymal stem cell-derived extracellular vesicles. This hydrogel significantly reduced ROS levels and decreased the survival rates of *Escherichia coli*, *Staphylococcus aureus*, and Pseudomonas aeruginosa to 4.6%, 4.3%, and 1.7%, respectively, indicating strong antioxidant and antibacterial activities.[104]

Nanoparticles

Nanoparticles, typically defined as particles ranging from 1 to 100 nm in at least one dimension and composed of either inorganic or organic materials,[105] offer distinct advantages in the treatment of RISI. (1) Nanoparticles can encapsulate multiple bioactive agents to simultaneously exert antioxidant, anti-inflammatory, and pro-angiogenic effects; (2) Their nanoscale dimensions and high surface activity facilitate transdermal penetration, thereby enhancing drug absorption and bioavailability; (3) Surface modifications of nanoparticles enable targeted delivery, increasing local drug concentrations while minimizing systemic side effects.[106] Figure 5 provides an overview of the design strategies and therapeutic functions of both inorganic and organic nanoparticles for the treatment of RISI, serving as a valuable reference for the development of nanoparticles.

Inorganic Nanoparticles

Inorganic nanoparticles are functional nanomaterials composed of metals or metal oxides, nonmetals and their derivatives.[107] Silver nanoparticles (Ag NPs) are a class of metallic nanomaterials widely utilized in wound healing due to their potent antimicrobial properties. They exert antibacterial effect by directly compromising the integrity of bacterial cell walls and releasing silver ions, which bind to microbial thiol groups, DNA, and enzymes, thereby disrupting essential metabolic pathways.[108] A clinical study showed that the incidence of radiation dermatitis in the control group after radiotherapy was 100%, while the incidence of radiation dermatitis in the observation group coated with nano-silver antimicrobial gel was 76.9%, indicating that nano-silver antimicrobial gel can significantly reduce the incidence of radiation dermatitis.[109] Copper-based nanoparticles have been shown to be one of the ideal candidates for wound dressing. Copper is involved in various stages of wound healing, especially in the regulation of cytokine modulation and growth factor signaling pathways. It can also promote skin tissue regeneration and vascular network construction, which is beneficial for wound repair. Dong et al synthesized PC@CuS nanoparticles by coordinating phycocyanin with Cu^{2}+ and S^{2-}. These copper-based nanoparticles exhibited excellent ROS scavenging and antibacterial activities in vitro. When applied to a murine model of RISI, PC@CuS treatment resulted in complete re-epithelialization and maximal angiogenesis by day 25, accompanied by full wound closure, indicating a significant promotive effect on wound healing.[11]

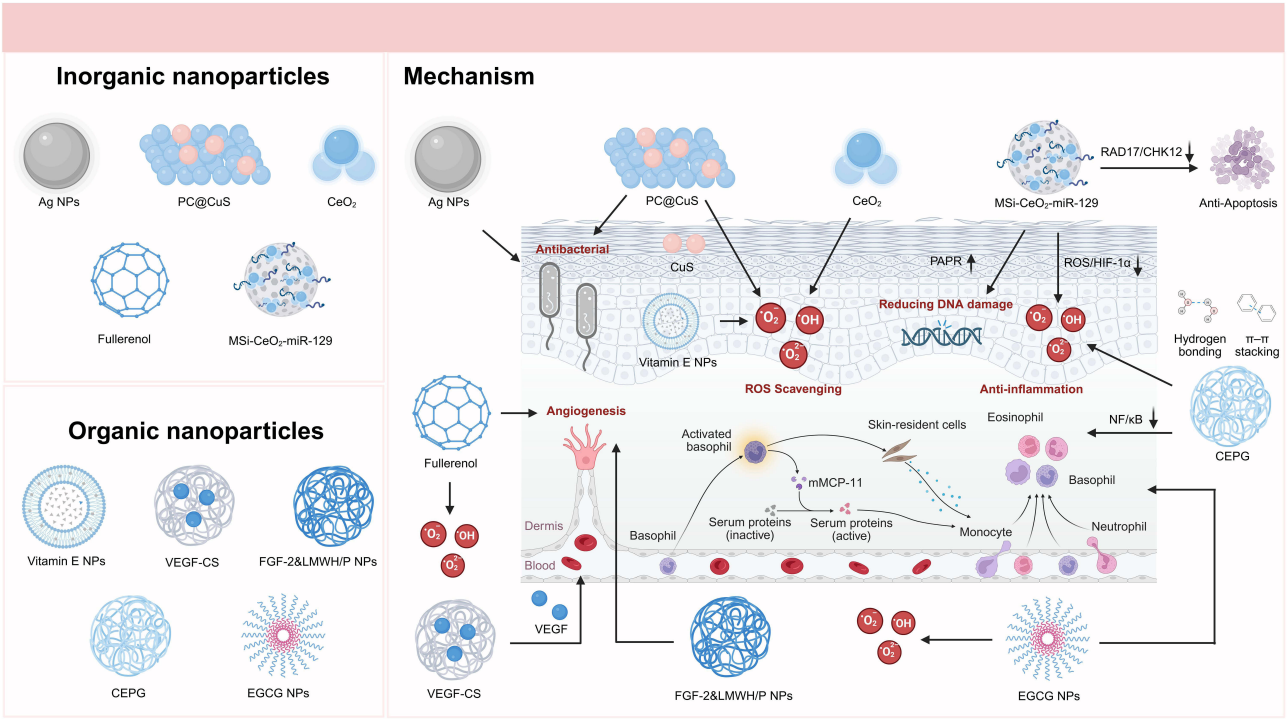

Figure 5 The design and function of nanoparticles for the treatment of RISI. (Created with https:BioRender.com).
Abbreviations: RAD17, Radiation sensitive 17; CHK1/2, Checkpoint kinase 1/2; PARP, Poly (ADP-ribose) polymerase; ROS, Reactive oxygen species; HIF-1α, Hypoxia-inducible factor 1 alpha; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; mMCP-11, Mouse mast cell protease 11; VEGF, Vascular endothelial growth factor.

Metal oxides are inorganic materials composed of metal and oxygen elements, including cerium oxide, zinc oxide, and iron oxide.[110] Among these, cerium oxide nanoparticles have emerged as widely used radioprotective materials due to their unique electronic structure and multifunctionality. The abundant oxygen vacancies and the ability of cerium to switch between +3 and +4 valence states enable efficient scavenging of free electrons and holes generated by radiation.[111] Rafael A. Madero-Visbal et al found that the incidence of RISI in mice treated with normal saline and cerium oxide nanoparticles was 100% and 10%, respectively, indicating that cerium oxide nanoparticles have significant efficacy.[112]

Non-metallic materials, particularly carbon-based and silicon-based compounds, have attracted increasing attention in the field of radiation protection. For example, fullerene is an all-carbon molecule with a cage-like structure, characterized by exceptional stability, unique electronic properties, and strong antioxidant capacity. Unlike conventional antioxidants that neutralize free radicals through direct chemical reactions, fullerenes scavenge free radicals by capturing their unpaired electrons without being consumed in the process.[113] Peng et al developed a transdermal fullerenol emulsion, which exhibited both antioxidant and pro-angiogenic activities.[114] Silicon dioxide is a widely studied silicon-based nanomaterial with significant potential in wound healing applications. Its high specific surface area, porous structure, and chemical stability make it an excellent carrier for drug delivery. Moreover, silica directly contributes to the wound healing process by releasing bioactive silicic acid, which has been shown to promote cell proliferation and migration in injured tissues.[115] Zhou et al developed a novel cerium oxide nanoparticle-anchored mesoporous silica nanocomposite for enhanced delivery of miR-129 (MS-CeO_2-miR-129). This nanocomposite attenuated ROS levels and HIF-1α expression in RISI. By targeting RAD17 and modulating the CHK2 signaling pathway, it reduced radiation-induced apoptosis, while simultaneously modulating poly(ADP-ribose) polymerase (PARP) expression to facilitate DNA repair, ultimately promoting high-quality wound healing.[116]

Organic Nanoparticles

A variety of organic nanoparticles with multiple functional activities have been developed, including lipid nanoparticles, polymeric nanoparticles, and those derived from plant-based bioactive compounds.[117]

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Lipid nanoparticles, typically composed of lipid vesicles with a uniform lipid core, have gained considerable attention in recent years due to their successful applications in mRNA vaccines and gene therapy.[106] Various forms of lipid nanoparticles have been developed, including liposomes, solid lipid nanoparticles, and nanostructured lipid carriers. Classical lipid nanoparticles are primarily composed of ionizable cationic lipids, cholesterol, phospholipids, and polyethylene glycol-lipid. This composition imparts excellent biocompatibility, biodegradability, and high drug encapsulation efficiency, making lipid nanoparticles highly promising candidate for the treatment of RISI.[118] A randomized, triple-blind, controlled clinical pilot trial evaluated the efficacy of a topical cream containing vitamin E-loaded lipid nanoparticles for the prevention of radiation-induced dermatitis in breast cancer patients. The results demonstrated that the formulation effectively attenuated oxidative stress damage and reduced the incidence of radiation dermatitis.[73]

Polymer nanoparticles are gelatinous carrier systems formed from natural or synthetic polymers that encapsulate drugs in the core or adsorb them to the surface, maintaining a sustained release of the drug and reducing the frequency of administration.[119] Polymer nanoparticles exhibit excellent biocompatibility and biodegradability, along with greater physicochemical stability compared to lipid nanoparticles. Polymers such as chitosan, gelatin, polylactic acid, poly (lactic-co-glycolic acid), and proteins represent the principal materials utilized in the preparation of polymer nanoparticles.[120] Yu et al developed chitosan-based nanoparticles encapsulating vascular endothelial growth factor, which enabled sustained release of VEGF for up to 30 days, effectively addressing the challenge of its short half-life. Animal studies demonstrated that VEGF-CS nanoparticles effectively inhibited vascular endothelial cell apoptosis and promoted angiogenesis, which in turn delayed the progression of RISI and facilitated wound healing.[81] Fibroblast Growth Factor −2 (FGF-2), despite its radioprotective properties, is highly susceptible to degradation by heat and proteolytic enzymes in vivo. To enhance its stability and prolong its therapeutic effect, researchers developed low molecular weight heparin/fish protein-based nanoparticles (FGF-2 and LMWH/P NPs) as a delivery system. When applied for the treatment of RISI, the nanoparticles led to a significant reduction in apoptotic dermal fibroblasts, along with enhanced blood vessel formation and an improved wound healing rate observed on days 3, 7, and 14, as compared to the irradiated group without treatment.[121]

Plant-derived compounds such as curcumin, catechin, and quercetin offer new options for the treatment of RISI due to their antioxidant, anti-inflammatory, and antibacterial properties.[122] Notably, using self-assembly techniques, nanoprecipitation, and emulsion polymerization, these compounds can be formulated into nanoparticles to enhance their own solubility, bioavailability, and pharmacological efficacy. For instance, EGCG and curcumin suffer from poor bioavailability and instability. However, they can be co-assembled into polyphenol nanoparticles (CEPG) via intermolecular hydrogen bonding and π–π stacking interactions, resulting in improved stability along with potent anti-inflammatory by blocking the NF-κB pathway.[123] Han et al proposed an alternative strategy by modifying EGCG with polyethylene glycol, enabling its self-assembly into EGCG nanoparticles. This modification enhanced cellular uptake and decreased ROS, ultimately mitigating radiation-induced skin edema and erythema.[124]

Nanofibers and Microneedles

Emerging materials such as nanofibers and microneedles have also been explored for the treatment of RISI (Figure 6). As nanoscale fibrous structures, nanofibers exhibit high porosity, large specific surface area, and favorable mechanical properties, making them suitable for use as wound dressings that facilitate gas exchange or as drug delivery systems.[125] For instance, electrospun micro/nanofiber patches incorporating an aqueous bark extract of *Pinus halepensis* Miller (PHBE), which is rich in antioxidant polyphenols, have demonstrated efficacy in the prevention of radiodermatitis. Compared to conventional clinical creams, PHBE patches exhibited superior anti-inflammatory activity and effectively restored skin parameters to normal levels, thereby reducing patient discomfort.[126] Notably, nanofibers can also be engineered to structurally mimic bioactive factors and elicit comparable biological functions. PDGF plays a key role in promoting cell proliferation, migration, and anti-apoptotic signaling. Shang et al engineered the first supramolecular nanofiber based on the self-assembling peptide Nap-FFGVRKKP. This nanofiber effectively engages the PDGF receptor by mimicking the β-sheet conformation of PDGF and the pentapeptide VRKKP in ring 3, thereby activating downstream RAS–MEK–ERK and PI3K–AKT–mTOR signaling pathways. Consequently, it promotes NIH 3T3 cell proliferation and markedly reduces irradiation-induced apoptosis from 33.60% to 5.83%, highlighting its potent therapeutic potential for RISI.[12]

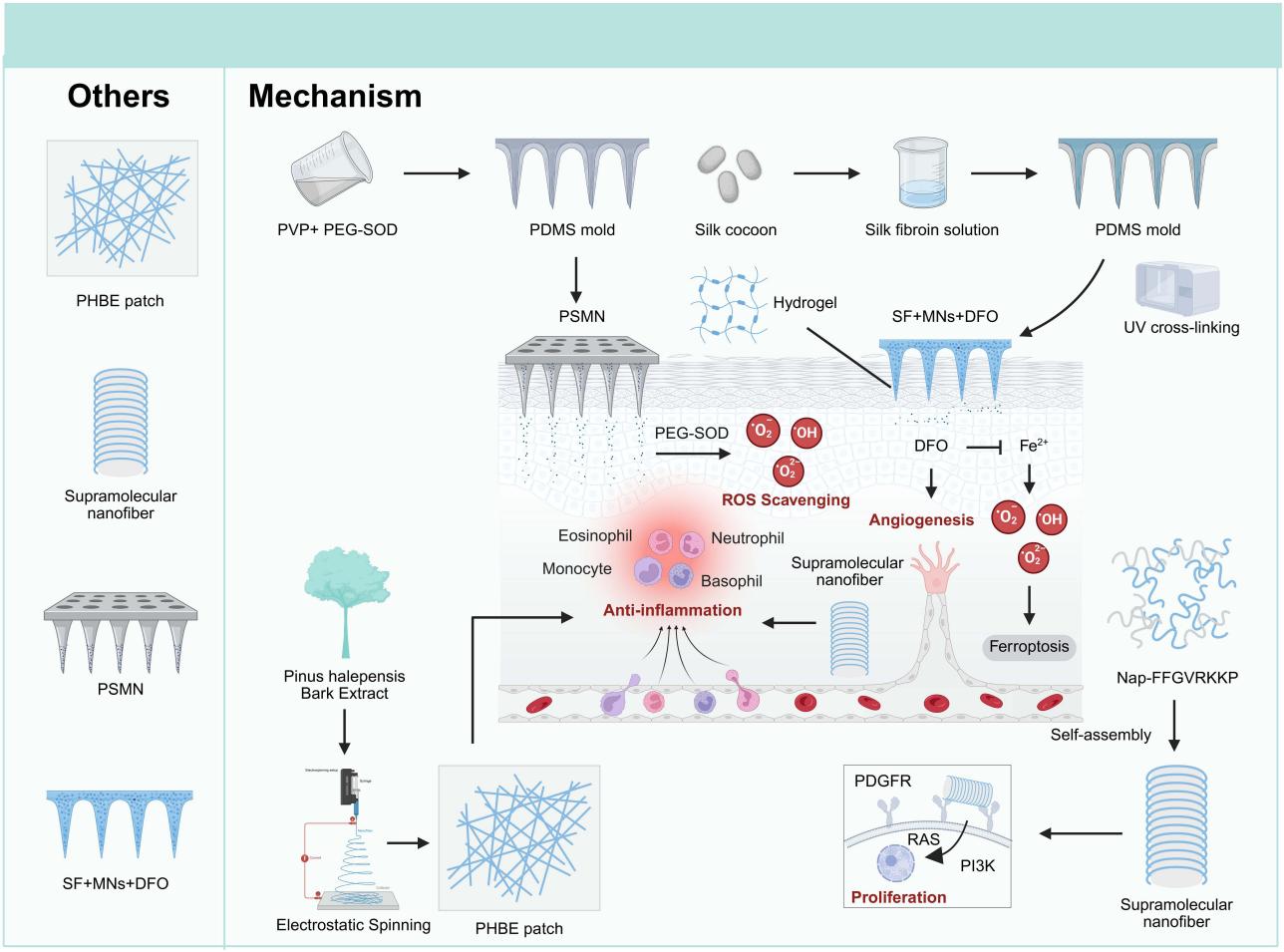

Figure 6 The design and function of nanofibers and microneedles for the treatment of RISI. (Created with https:BioRender.com).
Abbreviations: PDMS, Polydimethylsiloxane; PVP, Polyvinylpyrrolidone; PEG, Polyethylene glycol; SOD, Superoxide dismutase; DFO, Deferoxamine; RAS, Rat sarcoma oncogene; PI3K, Phosphoinositide 3-kinase; PHBE, *Pinus halepensis* bark extract.

The large size of traditional injection needles often affects patient adherence to treatment, leading to increased interest in micron-sized microneedles. Microneedles, typically ranging from 25 to 2500 μm in length, consist of either a single needle or an array of needles capable of penetrating the skin barrier.[127] These needles provide an efficient pathway for active drug delivery while avoiding direct contact with underlying nerve endings, thus minimizing pain during administration. One of the first studies to apply microneedles for RISI treatment was conducted by Ma et al. They addressed the limited skin permeability of polyethylene glycolated superoxide dismutase (PEG-SOD) by developing a microneedle system using the stencil-mold method. The results showed that the skin permeability of the microneedle was 500 times higher compared to PEG-SOD solution, enabling more effective free radical scavenging for preventing radiodermatitis.[128] Subsequently, Hu et al demonstrated that microneedle-mediated delivery of nanoparticles composed of EGCG and curcumin effectively facilitated direct penetration into epidermal keratinocytes and reduced cellular damage caused by free radicals.[123] Furthermore, Tian et al developed a hydrogel microneedle (SF+MNs) composed of silk fibroin and acrylamide for the delivery of desferrioxamine (DFO). This system effectively reduced oxidative stress associated with ferroptosis and promoted neovascularization. Notably, prophylactic administration of SF+MNs+DFO prior to radiation resulted in a wound healing rate exceeding 90% by day 10 post-irradiation.[13]

The innovative design of these biomaterials presents promising new strategies for the treatment of RISI. However, the application of nanofibers and microneedles in RISI remains limited. Major challenges include the complex fabrication processes and the rapid degradation of nanofibers, which compromise their therapeutic efficacy. Although microneedles

have shown effectiveness in certain cases, they are constrained by limited drug loading capacity, insufficient mechanical strength that increases the risk of fracture, and potential infection risks associated with transient disruption of the skin barrier.

Current Status of Clinical Transformation

In recent years, several biomaterials have achieved initial clinical progress in the management of RISI (Table 3). Hydrogel-based materials such as Hydrosorb® have advanced to Phase III clinical trials and demonstrated the ability to relieve patient pain, although no significant improvement has been observed in the treatment of acute RISI. In addition, the application of the film-forming silicone gel StrataXRT® has been shown to reduce both the erythema index and the melanin index in patients with RISI.[129] Additional products, including Radiation Care®, RadiaAce Gel, and the Bacterial Cellulose–Monolaurin Hydrogel, have entered clinical evaluation. Some nanoparticles, such as nano-curcumin, have undergone clinical observational evaluation, which demonstrated a reduction in RISI severity by the seventh week

Table 3 The Advantages, Limitations, Application Scenarios, and Clinical Progress of Each Delivery System

Delivery System	Advantages	Limitations	Applicable Scenarios	Clinical Cases	Transformation Stage	Reference
Hydrogels	Moisture retention, high biocompatibility, and easy clinical handling	Bacterial susceptibility and low mechanical strength	Exudative and irregular wounds	Hydrosorb®	Phase III Trial	NCT02839473
				Radiation Care®	Not Applicable	NCT04995328
				StrataXRT®	Not Applicable	NCT05073172
				RadiaAce Gel	Not Applicable	NCT04481802
				Bacterial Cellulose-monolaurin Hydrogel	Phase II Trial	NCT05079763
Nanoparticles	High delivery efficiency and good skin permeability	Potential cytotoxicity and challenges in GMP-grade production and scale-up	Therapy for deep skin lesions and targeted treatment requirements	ROS-scavenging Amino Acid-derived Lipids	Not Applicable	NCT07081074
				Nano-Curcumin	Observational clinical study	[130]
				Vitamin E-loaded lipid nanoparticles	Observational clinical study	[73]
Nanofibers	High drug-loading capacity, Favorable mechanical properties, and Supportive microenvironment for cell adhesion and growth	High manufacturing cost and Residual solvent toxicity risk	Chronic or non-healing wounds and therapies requiring enhanced mechanical support	PHBE patches	Observational clinical study	[126]
Microneedles	High delivery efficiency, strong skin permeability, and good patient compliance	Low drug-loading capacity, insufficient mechanical strength, and infection risk	Limited transdermal transport of drugs a nd suitable for low-pain, long-term therapy	Desferrioxamine microneedles	Basic Research	[13]

Notes: Not applicable, used for trials that do not involve drug or biologic products subject to FDA regulation and thus are not conducted under an FDA-defined phase, Phase I–IV).

Abbreviation: PHBE, *Pinus halepensis* Miller extract.

together with marked pain relief.[130] Another multicenter randomized trial will evaluate the efficacy and safety of ROS-scavenging amino-acid-derived lipids in alleviating RISI. Nanofibers and microneedles used for treating RISI remain mainly at the basic research stage. These examples collectively underscore the translational promise of biomaterials, yet their clinical application remains constrained by several critical limitations.

(1) Scalability and GMP manufacturing: Current fabrication strategies for biomaterials largely rely on laboratory-scale protocols, and substantial challenges arise when scaling up to industrial production. For GelMA, parameters such as grafting efficiency and precursor concentration are difficult to control precisely during scale-up, leading to inter-batch variations of up to 10–20% in mechanical properties.[131] This highlights the difficulty of maintaining key quality attributes including crosslink density and biomechanical performance under GMP conditions.[132] Nanoparticle systems face analogous issues, as large-scale synthesis often induces heterogeneity in mixing, resulting in inconsistencies in particle size, encapsulation efficiency, and surface characteristics. Large-scale nanofiber fabrication is similarly affected by solvent evaporation-induced changes in polymer concentration and uneven distribution of active components, reducing the uniformity of fiber morphology and functional properties.[133] Microneedle production also presents persistent challenges, particularly in achieving mold reproducibility and ensuring uniform drug activity and spatial distribution during drying and solidification.[134]

(2) Sterilization: Sterility is a fundamental prerequisite for the clinical application of implantable or topical biomaterials. Conventional sterilization methods, including gamma irradiation, ethylene oxide treatment, and autoclaving, can disrupt polymer chains or alter the degree of crosslinking, leading to changes in mechanical properties and drug release profiles.[135] Moreover, biologically active components such as exosomes and growth factors are particularly susceptible to degradation or loss during these processes. Low-temperature supercritical CO_2 sterilization has been proposed as a gentler alternative, exerting comparatively minor effects on the mechanical and rheological properties of biomaterials.[136] Nevertheless, the general applicability of this approach and its ability to preserve the activity of sensitive bioactive components require systematic validation.

(3) Stability and shelf-life: The stability of biomaterials is a critical determinant for their clinical translation. To date, most studies have focused primarily on material fabrication and short-term efficacy evaluation, without systematically assessing potential changes during long-term storage. Such changes may include alterations in mechanical properties, drug release kinetics, and the activity of incorporated therapeutics, all of which are essential parameters for ensuring consistent performance and safety in clinical use.

(4) Regulatory pathways: In the FDA regulatory framework, combination products are defined as products comprising medical devices, drugs, or biological products that collectively achieve a clinical effect.[137,138] The FDA oversees these products through the Office of Combination Products and classifies them according to their primary mode of action (PMOA). Under 21 CFR 3.2(e), combination products are further categorized as single-entity, co-packaged, or cross-labeled types. The regulatory pathway is determined by the PMOA, which designates the lead review center, including CDER for drugs, CBER for biologics, or CDRH for medical devices.[139] In contrast, the EMA does not have a distinct classification for combination products, instead assigning them to either drug or device regulatory pathways based on the product's primary intended purpose. Under the Medical Device Regulation (MDR 2017/745), "drug-containing devices" must undergo scientific assessment by the relevant drug regulatory authority during the Conformité Européenne certification process, whereas "complete drug-device combinations" are evaluated according to drug regulations (2001/83/EC). Products incorporating cells, genes, or tissue-engineered components are classified as Advanced Therapy Medicinal Products and are reviewed by the Committee for Advanced Therapies, with any device components required to meet MDR standards.[140]

Regenerative Therapies

The emergence of regenerative therapies arises from the inherent limitations of conventional treatments in complex wound healing and the urgent demand for innovative approaches. Radiation-induced cellular and mitochondrial dysfunction disrupts the reparative process, while regenerative strategies such as stem cell therapy and mitochondrial transplantation seek to restore homeostasis and directly address the underlying causes, thereby supporting effective tissue repair.

Stem Cell Therapy

Stem cell therapy offers distinct advantages in RISI due to its regenerative potential and spatiotemporal adaptability. It refers to the transplantation of stem cells or their derivatives into the body to replace damaged cells, tissues or organs (Figure 7).[15] Adipose-derived stem cells (ADSCs), bone marrow-derived stem cells (BMSCs), and stromal vascular fraction (SVF) have shown efficacy in promoting wound repair in RISI. Table 4 summarizes the stem cell types, experimental models, mechanisms, and therapeutic outcomes reported in preclinical and clinical studies, aiming to provide a theoretical foundation for the application and clinical translation of stem cell therapy in RISI.

BMSCs

BMSCs are adult stem cells derived from bone marrow and represent one of the most widely used types of mesenchymal stem cells.[115] They exhibit robust proliferative and multipotent differentiation capacities, enabling differentiation into endothelial cells, fibroblasts, and adipocytes in vitro.[157] In addition, their homing ability allows targeted migration to sites of injury, where they contribute to wound closure and tissue remodeling.[158] BMSCs also promote angiogenesis and improve local microcirculation through paracrine secretion of factors such as VEGF and FGF-2. Kakabadze et al reported that a decellularized human amniotic membrane combined with lyophilized BMSCs retained paracrine activity and achieved a fourfold increase in wound healing rate.[141] Furthermore, BMSCs exert immunomodulatory effects by regulating the wound microenvironment, including suppression of PGE2 and TGF-β, upregulation of SDF-1, and promotion of macrophage polarization toward the M2 anti-inflammatory phenotype.[142] Furthermore, BMSCs participate in multiple signaling pathways during the repair of radiation- RISI. Specifically, they promote cell survival through

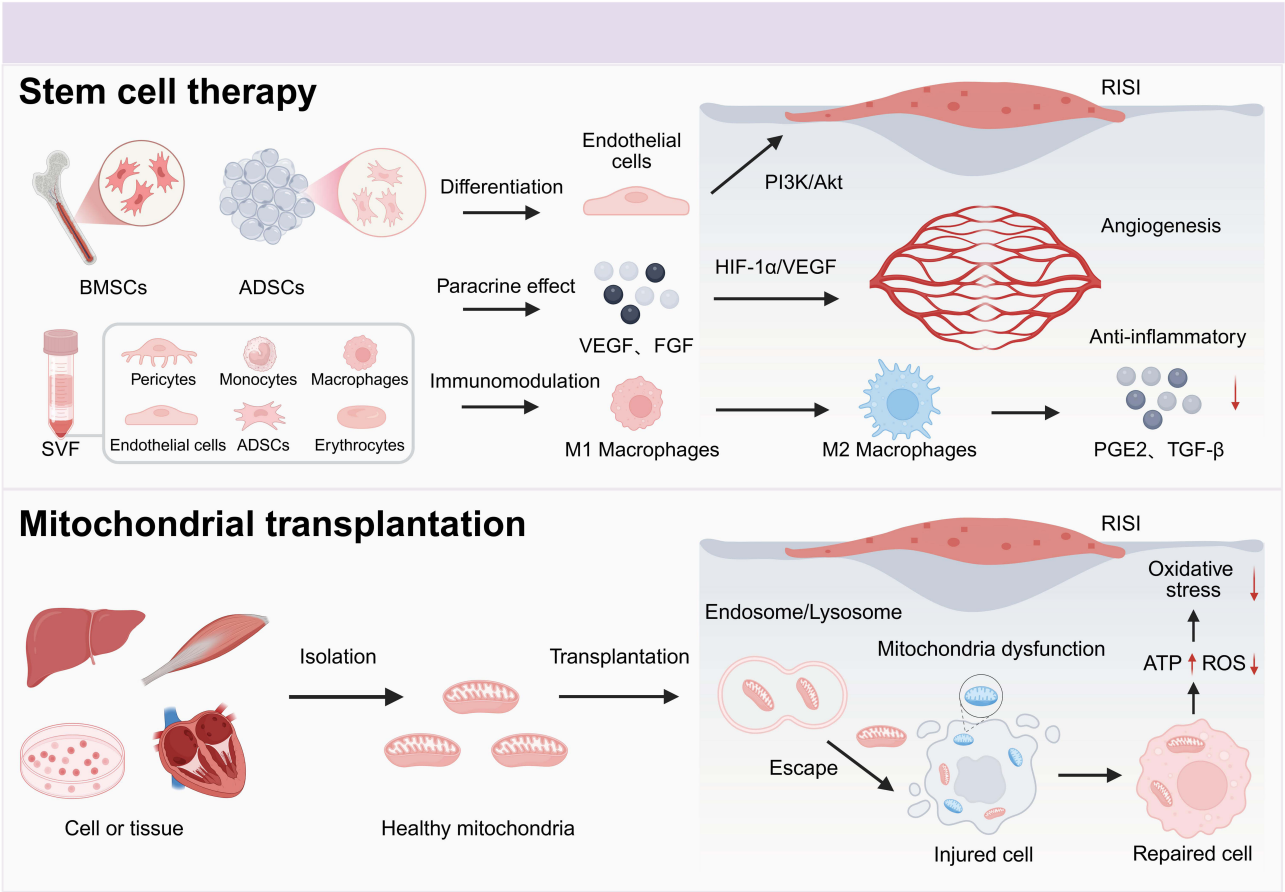

Figure 7 Stem cell therapy and mitochondrial transplantation for the treatment of RISI. (Created with https:BioRender.com).
Abbreviations: PI3K, Phosphoinositide 3-kinase; AKT, Protein kinase B; HIF-1α, Hypoxia-inducible factor 1 alpha; VEGF, Vascular endothelial growth factor.

Table 4 Stem Cell Types, Source, Mechanisms, Experimental Models, and Therapeutic Outcomes in Preclinical and Clinical Studies for the Treatment of RISI

Stem Cell Type	Source	Mechanisms	Experimental Models	Therapeutic Outcomes	References
BMSCs	Bone marrow	Mediating paracrine effects	Lewis inbred rats	Fourfold increase in wound healing rate	[141]
		Reducing PGE2 and TGF-β, increasing SDF-1	Sprague-Dawley rats	Reduction in skin damage and acceleration of wound healing	[142]
		Promoting M2 macrophage polarization	C3H/HeN mice	Reduction in skin contracture, thickening, and collagen deposition	[143]
		Homing characteristics	NOD/SCID mice	Homing of BMSCs to irradiated skin sites after infusion in mice	[144]
		Restoring calcineurin-6 and reducing MMPs	B6D2F1/J female mice	Increase in 30-day survival rate by 30% Reduction in weight loss and enhancement of wound healing	[145]
		Reducing c-reactive protein levels	Human	Absence of RISI recurrence during 8-month patient follow-up	[146]
ADSCs	Adipose tissue	Suppressing CTSF and modulating apoptotic proteins	Male Sprague-Dawley rats	Decrease in ulcer size and complete skin repair within 4 weeks after irradiation	[147]
		Inducing VEGF release and promoting re-epithelialization and angiogenesis	C57Bl/6 male mice	Acceleration of wound healing and improvement in skin elasticity	[148]
		Enhancing re-epithelialization, lymphocytic infiltration and angiogenesis	Göttingen minipigs	Wound healing in four-fifths of minipigs receiving transplants	[147]
		Downregulating fibrogenic genes and recruiting bone marrow cells to exert anti-fibrotic effects	Female C57BL/6J mice	Restoration of skin structure and attenuation of fibrosis	[149]
		/	Male nude mice	Acceleration of skin wound healing, with near-complete closure by day 12	[150]
		Increasing angiogenesis and granulation	Sprague–Dawley rats	Significant reduction in wound size	[151]
		Down-regulating inflammatory genes and fibrosis genes expression	Female C57BL/6J mouse	Improvement in advanced radiation-induced damage and fibrosis	[152]
		Promoting fibroblast proliferation and collagen synthesis	Human	Acceleration of wound healing	[153]

(*Continued*)

https://doi.org/10.2147/IJN.S568923

Table 4 (Continued).

Stem Cell Type	Source	Mechanisms	Experimental Models	Therapeutic Outcomes	References
SVF	Adipose tissue processed via mechanical or enzymatic dissociation	Increasing neoangiogenesis and reducing subcutaneous sclerosis	Male or female nude NMRI-Foxnu1nu/nu mice	Enhancement of angiogenesis with limited improvement in wound healing rate	[154]
		Stimulating secretion of collagen, MMP-1, and other proteins	Male Sprague-Dawley rats	Reduction in skin damage caused by electron beam radiation	[155]
		/	Human	Progressive wound healing without recurrence, accompanied by effective pain relief and restoration of skin integrity	[155]
		/	Human	Complete recovery of the epidermis without significant pain or abnormalities	[156]

Abbreviations: PGE2, prostaglandin E2; SDF-1, stromal cell-derived factor 1; CTSF, cathepsin F; MMP-1, matrix metalloproteinase-1.

activation of the PI3K/Akt pathway,[159] enhance angiogenesis via modulation of the HIF-1α/VEGF axis,[160] and attenuate fibrosis by inhibiting TGF-β/Smad signaling, collectively facilitating tissue regeneration.[161]

Several preclinical and clinical studies have confirmed the therapeutic efficacy of BMSCs in RISI. For instance, Sabine François et al demonstrated that systemically infused BMSCs specifically homed to irradiated skin sites in mice and contributed to tissue repair.[144] Kiang et al reported that BMSC-treated irradiated mice exhibited a 30% increase in survival rate along with significantly accelerated wound healing.[145] In one clinical study, repeated transfusions of autologous unirradiated bone marrow-derived BMSCs were used to treat patients with severe RISI. No recurrence was observed during the 8-month follow-up, suggesting that BMSCs may act as "drug cells" in the treatment of RISI.[146]

However, the clinical translation of BMSCs still faces challenges such as the difficulty of cell isolation and limited yield, which makes it difficult to meet the large-scale therapeutic demand. Meanwhile, their long-term safety in RISI treatment needs to be further evaluated to ensure the feasibility and safety of clinical application.

ADSCs

ADSCs, derived from adipose tissue, are typically obtained through liposuction. Compared to BMSCs, ADSCs possess several significant advantages, including a more abundant source, low immunogenicity, and a minimally invasive harvesting procedure with an extraction quantity approximately 500 times greater than that of BMSCs.[162] These features make ADSCs an ideal candidate for the treatment of RISI.

ADSCs possess the capacity to differentiate into epithelial and endothelial cells under specific conditions, thereby contributing to the repair of skin tissue.[163] Additionally, ADSCs promote epidermal cell migration and regeneration via activation of the Wnt/β-catenin signaling pathway.[164] They also secrete various angiogenic factors, including VEGF, hepatocyte growth factor (HGF), and FGF, which promote neovascularization and re-epithelialization, ultimately accelerating the wound healing process.[165] Moreover, ADSCs stimulate the proliferation of human dermal fibroblasts and promote extracellular matrix deposition through intercellular contact or the secretion of paracrine factors, thereby facilitating dermal tissue remodeling.[148] Its regulation of extracellular matrix remodeling is closely associated with alterations in the expression of fibrosis-related markers, including matrix metalloproteinase-9 (MMP-9), collagen type I alpha 1 chain (COL1A1), and alpha-smooth muscle actin (α-SMA).[166] By inhibiting CTSF expression, ADSCs can effectively reduce radiation-induced apoptosis and enhance hair follicle regeneration. Exosomes derived from ADSCs also serve as crucial mediators in promoting wound repair. These exosomes regulate the autophagy signaling pathway via

the Neat1/miR-17-5p/Ulk1 axis, facilitating the clearance of damaged cells.[167] Additionally, they contribute to tissue repair and regeneration by downregulating the expression of pro-inflammatory cytokines such as IL-6 and TNF-α, promoting macrophage polarization toward a reparative phenotype, enhancing the release of interleukin-33 (IL-33), and stimulating keratinocyte proliferation and collagen deposition.[168]

The therapeutic efficacy of ADSCs in the treatment of RISI has been validated in various animal models. Wu et al demonstrated that mice with radiation-induced skin wounds treated with ADSC injections exhibited accelerated wound healing, with nearly complete healing observed by day 12.[150] Huang et al showed that ADSC transplantation for the treatment of RISI in mice over a 3-week period led to a significant increase in capillary density within the dermis and enhanced dermal thickness in the healing skin. This improved blood supply to the wound site and promoted granulation tissue formation, which in turn accelerated wound healing.[151] Malekzadeh et al reported that ADSCs reduced the expression of inflammatory genes and fibrogenic genes in human fibroblasts, therefore mitigating late radiation-induced injury. These effects were observed in both autologous and allogeneic ADSC transplantations in irradiated mice.[152] Furthermore, in a minipig model, autologous ADSC transplantation significantly enhanced re-epithelialization, lymphocyte infiltration, and angiogenesis, ultimately resulting in complete wound healing in four out of five treated animals.[147]

In summary, ADSCs exhibit multiple wound-healing properties, including the promotion of cell proliferation, angiogenesis, and anti-inflammatory effects. Notably, ADSCs can be isolated from autologous adipose tissue, thereby reducing the risk of immune rejection. Their safety and non-tumorigenic nature further support their potential as a promising cell source for autologous stem cell transplantation therapy.

SVF

SVF is emerging as a novel therapeutic component in stem cell-based therapies. It comprises a heterogeneous mixture of cells and stromal elements isolated from adipose tissue, including ADSCs, endothelial cells, macrophages, monocytes, and other cell types.[169] SVF offers several advantages, including direct application without in vitro expansion, high cell yield, and low immunogenicity.[170]

SVF mediates tissue repair through complementary mechanisms. ADSCs and endothelial progenitor cells within SVF not only differentiate into epidermal and vascular endothelial cells but also secrete pro-angiogenic factors that promote neovascularization and tissue regeneration. Compared with single ADSCs, SVF possesses higher angiogenic potential, which significantly enhances capillary density and improves local microcirculation.[171] Immune cell subsets, such as macrophages and monocytes, contribute to the regulation of the wound microenvironment by suppressing pro-inflammatory cytokines including IL-6 and TNF-α, thereby attenuating chronic inflammation.[172] Moreover, SVF enhances fibroblast activity by stimulating the secretion of collagen and matrix metalloproteinase-1 (MMP-1) and by inhibiting TGF-β-driven fibrotic processes, thereby supporting extracellular matrix remodeling and promoting skin regeneration.[173]

Multiple studies have confirmed the therapeutic potential of SVF for RISI. Bertrand et al found that injecting SVF after irradiation in mice significantly increased the density of new blood vessels, but showed poor results in skin ulcer healing.[154] A rat model demonstrated that SVF treatment mitigated skin damage caused by electron beam radiation.[155] Iddins et al reported a case of locally recurrent radiation-induced skin injury, in which the wound was treated with autologous SVF for 11 months. The epidermis of patients recovered completely, with no significant pain or abnormalities, suggesting the potential for long-term benefits from SVF therapy.[156] Furthermore, Yu et al reported that five patients with RISI treated with SVF grafts exhibited gradual wound healing, with no recurrence, pain relief, and overall improvement in skin condition.[155]

In conclusion, SVF offers a promising new strategy for the repair of RISI due to its diverse therapeutic properties, the safety associated with its autologous origin, and its low immunogenicity. However, its complex cellular composition, inter-individual variability, and long-term safety remain areas that require further investigation.

Although stem cell therapy holds considerable promise for promoting tissue regeneration, its clinical application faces substantial challenges. First, the efficiency of cell engraftment remains relatively low, owing to poor post-transplant survival, limited homing, and inadequate long-term retention. Second, while autologous cells exhibit low immunogenicity, allogeneic or genetically modified cells may still elicit immune rejection, compromising their functional persistence

in vivo. Therefore, future efforts should focus on enhancing in vivo cell survival and optimizing immune modulation strategies to facilitate the clinical translation of stem cell therapies.

Mitochondrial Transplantation

Mitochondria are semi-autonomous organelles found in eukaryotic cells that function as cellular "energy factories", generating ATP via oxidative phosphorylation to fulfill the metabolic demands of the cell. Beyond energy metabolism, mitochondria are integral to calcium homeostasis, intracellular signaling, and the regulation of apoptotic pathways.[174] Interestingly, recent studies have highlighted the role of intercellular mitochondrial transfer in modulating metabolic homeostasis, adjusting mitochondrial content in donor cells, and influencing wound healing.[175] For instance, brown adipocytes are capable of expelling damaged mitochondria, which are subsequently cleared by resident macrophages to preserve their thermogenic function.[176] Similarly, platelets have been shown to transfer functional mitochondria to mesenchymal stem cells, thereby enhancing the secretion of pro-angiogenic factors and accelerating the wound healing process.[177] However, these mitochondrial functions are severely disrupted in RISI, characterized by mtDNA fragmentation, impaired oxidative phosphorylation, and increased mitochondrial membrane permeability.[178] More importantly, such mitochondrial dysfunction plays a key role in ionizing radiation-induced cellular damage. For example, the release of fragmented mtDNA can activate the cGAS–STING pathway, initiating an inflammatory response, while sustained mitochondrial ROS production further amplifies oxidative stress.[179]

To address mitochondrial dysfunction at its source, mitochondrial transplantation has emerged as a promising therapeutic strategy. It refers to the isolation of healthy mitochondria from cells or tissues and delivered into damaged cells in order to restore mitochondrial function in the recipient cells, thereby ameliorating the disease (Figure 7).[180] This strategy enhances ATP production in recipient cells and improves cellular energy metabolism. It also modulates signaling pathways such as MAPK/ERK and PI3K/Akt to promote cell survival and regeneration. Furthermore, mitochondrial transplantation reduces the expression of the MAPK family member p-JNK, which in turn regulates apoptosis and inflammatory responses.[181] Yao et al developed a hydrogel microneedle patch for the delivery of mitochondria-enriched extracellular vesicles derived from stem cells to enhance the healing of RISI. The team first utilized metformin to stimulate adipose-derived stem cells, thereby increasing the mitochondrial content within the extracellular vesicles (Met-EVs). These Met-EVs were shown to mitigate X-ray-induced mitochondrial dysfunction in macrophages by transferring active mitochondria, which resulted in elevated ATP production and reduced ROS generation. Finally, incorporation of Met-EVs into the patch enabled direct mitochondrial delivery to the damaged skin site, significantly accelerating wound repair by day 12. This healing rate was comparable to that of the non-irradiated control group, demonstrating the favorable therapeutic potential of mitochondrial transplantation in the treatment of RISI.[182]

However, other components within extracellular vesicles, such as RNA or mtDNA, may also contribute to the therapeutic effects. In addition, the mechanisms governing the entry of exogenous mitochondria into target cells, the rate of uptake, their intracellular distribution, and their integration with endogenous mitochondria, all aspects related to mitochondrial kinetics, remain to be fully elucidated. Furthermore, further preclinical studies and clinical trials are essential to assess the biological effects and potential risks.

Conclusions and Future Prospects

RISI is a common complication following tumor radiotherapy and nuclear radiation exposure, characterized by a multifaceted mechanism involving oxidative stress, DNA damage, inflammation, defective angiogenesis and fibrosis, and microbiome dysregulation. Current therapeutic options remain limited in efficacy, highlighting the urgent need for innovative and more effective treatment strategies. Biomaterials have emerged as promising candidates for RISI management, owing to their versatility, tunability, and excellent biocompatibility. In parallel, the regenerative therapies that use healthy cells or mitochondria to replace damaged objects can address the disease at the source, providing a regenerative strategy for the treatment of RISI.

Despite notable progress in the use of biomaterials and regenerative therapies for the treatment of RISI, several critical challenges remain to be solved:

1. The pathological progression of RISI is dynamic, with distinct therapeutic demands emerging at different stages of tissue repair. Therefore, future research should prioritize the development of intelligent biomaterials with spatiotemporal responsiveness, allowing them to dynamically adapt to fluctuations in the wound microenvironment. For example, endogenous stimuli responsive systems such as ROS sensitive switches, enzyme cleavable linkers, and pH responsive polymers can be engineered to achieve automated and on demand drug release in response to oxidative stress, inflammation, or local pH variations during the RISI repair process. In addition, exogenous stimuli responsive strategies that utilize acoustic, light, thermal, or electromagnetic cues can be incorporated to activate drug release at precise times and locations, thereby enabling accurate and controllable therapeutic intervention.
2. The cell sources, specific mechanisms of action, and long-term safety profiles of regenerative therapies still require further investigation. It will be essential to establish standardized screening systems for cell sources and to perform comprehensive long-term safety evaluations. Meanwhile, multi-omics analyses can be used to clarify the mechanisms and functions of transplanted cells or mitochondria within the injured microenvironment.
3. Biomaterials and regenerative therapies each offer distinct advantages in the treatment of RISI. A key direction for future research lies in the development of integrated therapeutic platforms, such as incorporating stem cells or mitochondria into functionalized hydrogels or microneedles, to achieve synergistic multifunctionality and promote regenerative repair.

In conclusion, both biomaterials and regenerative therapies offer significant potential for the treatment of RISI. By overcoming current challenges and accelerating the translation of basic research into clinical practice, it is expected to provide more effective and safer therapeutic strategies for the treatment of RISI in the future.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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