

REVIEW ARTICLE

Recent advances and challenges in 3D bioprinting for skin tissue regeneration

Supplementary File

Table S1. Comparative analysis of natural polymer biomaterials for 3D bioprinting applications

Material	Properties	Advantages	Limitations	Applications	Reference
Collagen	High biocompatibility; natural ECM mimicry; low mechanical strength	Supports cell adhesion and proliferation; biodegradable and non-toxic	Rapid degradation <i>in vivo</i> ; poor structural stability; high cost	Epidermal/dermal layer fabrication; vascularized constructs	^{1,2}
Gelatin	Thermoresponsive gelation; RGD motifs for cell adhesion	Low immunogenicity; cost-effective; tunable viscosity	Weak mechanical properties; requires chemical crosslinking (e.g., GelMA)	Sacrificial microchannels; multi-layered skin models	^{3,4}
Fibrinogen	Natural role in wound healing; polymerizes to fibrin via thrombin	Enhances cell migration and angiogenesis; biodegradable	Rapid degradation; batch-to-batch variability	Wound dressings; vascular network integration	^{5,6}
Alginate	Ionic crosslinking (Ca ²⁺); high printability	Rapid gelation; structural support for thick tissues	Lacks cell-adhesive motifs; requires RGD modification	Temporary scaffolds; hybrid bioinks for mechanical reinforcement	^{6,7}
Chitosan	Antibacterial properties; positively charged polysaccharide	Hemostatic and antimicrobial effects; enhances wound healing	Poor solubility at neutral pH; low cell adhesion	Antimicrobial wound dressings, composite bioinks for infection-prone wounds	^{8,9}
Hyaluronic acid	High hydrophilicity; ECM component in skin	Promotes tissue hydration; supports fibroblast migration	Low mechanical strength; fast degradation	Anti-scarring hydrogels; epidermal regeneration	^{9,10}
Decellularized ECM (dECM)	Native ECM composition; growth factor retention	High bioactivity; patient-specific compatibility	Complex preparation; risk of pathogen transmission	Full-thickness skin substitutes; vascularized and innervated constructs	^{11,12}
Silk fibroin	High tensile strength; tunable degradation rate	Excellent mechanical properties; biocompatible	Requires harsh processing solvents; slow gelation	Load-bearing skin scaffolds; nerve conduit fabrication	^{13,14}

Abbreviations: dECM: Decellularized extracellular matrix; ECM: Extracellular matrix; GelMA: Gelatin methacryloyl; RGD: Arginine–glycine–aspartic acid.

Table S2. The main cell types and functions of 3D bioprinting for skin repair

Cell Type	Characteristics	Primary Functions	Applications	Advantages	Limitations	Reference
Keratinocytes	Epidermal progenitor cells; express cytokeratins	Re-epithelialization; barrier formation; wound closure	Epidermal layer reconstruction; chronic wound healing (e.g., burns, ulcers)	Rapid proliferation; autologous sourcing possible	Limited ECM production; sensitive to shear stress during printing	15,16
Fibroblasts	Dermal ECM-producing cells; secrete collagen, fibronectin, and growth factors	ECM synthesis; granulation tissue formation; scar modulation	Dermal regeneration; hypertrophic scar reduction	Enhance mechanical stability; promote angiogenesis	Risk of fibrosis if overactivated	5,17
ECs	Line blood vessels; express CD31 and vWF	Vascular network formation; nutrient/oxygen delivery	Vascularized skin substitutes; diabetic wound healing	Enable perfusion of thick constructs; reduce necrosis	Low survival in hypoxic conditions; complex co-culture requirements	18,19
Melanocytes	Melanin-producing cells; localized in the epidermal basal layer	Skin pigmentation; UV protection	Pigmentation restoration; cosmetic reconstruction (e.g., vitiligo)	Improve aesthetic outcomes; patient-specific matching	Limited proliferation capacity; sensitive to oxidative stress	20,21
MSCs	Multipotent stromal cells; paracrine signaling; may be derived from bone marrow (BM-MSCs), adipose tissue (ADSCs), umbilical cord, or other sources	Anti-inflammatory effects; ECM remodeling; differentiation into skin cells	Chronic wound healing; scarless regeneration	Immunomodulatory properties; versatile differentiation potential	Heterogeneous cell populations; risk of uncontrolled differentiation	22,23
ADSCs (MSC subtype)	MSC subtype isolated from adipose tissue; fulfills ISCT MSC criteria (plastic adherence, surface markers CD73/CD90/CD105 ⁺ , multipotent differentiation); easily accessible; high proliferative capacity	Secrete angiogenic factors (e.g., VEGF); support nerve regeneration; anti-inflammatory and immunomodulatory effects consistent with MSC lineage	Diabetic ulcers; burn repair with appendage regeneration	Abundant source (adipose tissue); low immunogenicity; superior accessibility compared to BM-MSCs	Variable efficacy based on donor age/health	24-26
Schwann cells	Glial cells of the peripheral nervous system	Axonal guidance; neurotrophic factor secretion (e.g., NGF, BDNF)	Innervated skin substitutes; peripheral nerve repair	Critical for sensory recovery; enhance neurite outgrowth	Difficult to isolate and expand <i>in vitro</i>	27,28

Abbreviations: ADSCs: Adipose-derived stem cells; BDNF: Brain-derived neurotrophic factor; BM-MSCs: Bone marrow-derived mesenchymal stem cells; ECM: Extracellular matrix; ECs: Endothelial cells; ISCT: International Society for Cell & Gene Therapy; MSCs: Mesenchymal stem cells; NGF: Nerve growth factor; UV: Ultraviolet; VEGF: Vascular endothelial growth factor; vWF: von Willebrand factor.

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