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Study on the Effect of Scaffold Carriers on Tissue Repair and Rehabilitation in Cellular Environment

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ABSTRACT

Scaffold carriers are three dimensional porous biomaterial structures that provide structural support, metabolic signalling and an appropriate cellular environment for tissue regeneration. This article covers the effects of scaffold carrier mechanisms on tissue healing and rehabilitation in three key tissue systems: bone and cartilage, skin and soft tissue and neural tissue. This review integrates principles of extracellular matrix (ECM) biomimicry, scaffold material classification frameworks and cell-scaffold mechanotransduction theory, and uses evidence from in vitro and in vivo studies to illustrate how the scaffold architecture, material composition, surface chemistry and degradation kinetics collectively dictate the cellular responses (adhesion, proliferation and directed differentiation) that underlie functional tissue regeneration. Major design challenges, such as immunogenicity, inadequate vascularisation and degradation–regeneration kinetic mismatch, are comprehensively discussed. Finally, the paper explores the emerging concept of stimulus-responsive smart scaffolds as the next-generation technique to dynamically recapitulate the natural ECM environment and overcome translational restrictions that now hinder clinical use.

KEYWORDS

Scaffold carriers; Tissue repair; Tissue engineering; Extracellular matrix; Cell-scaffold interaction; Bone regeneration; Wound healing; Neural regeneration; Biomaterials; Smart scaffolds

1. INTRODUCTION

1.1. Research Background

Loss of tissue from trauma, degenerative sickness, surgical resection, and congenital deformity is a major clinical burden in modern medicine. Despite well-documented limitations including donor site morbidity, limited tissue supply and risk of immunological rejection in allogeneic transplantation, autologous tissue grafting remains the gold standard for repair. Tissue engineering science applies the principles of cell biology, materials science and engineering to create biological substitutes that restore or replace the function of damaged tissue. It has become the dominant scientific paradigm for the development of viable alternatives to traditional grafting procedures. In this context, scaffold carriers play a strategic role in providing the three-dimensional physical structure that directs cell organisation, the surface chemistry that mediates cell adhesion and signalling, and the mechanical properties that transduce the biomechanical forces that regulate cellular differentiation and tissue maturation.

The scaffold carriers function in a cellular setting that is not a passive substrate, but rather an active and dynamic milieu, and its biochemical and biophysical properties continuously influence cell activity via mechanotransduction, paracrine signalling, and ECM-receptor interactions. Thus, understanding the ways in which scaffold carriers interact with this cellular milieu is vital in rationally

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designing the next generation of scaffold systems with enhanced regeneration efficacy. Although significant breakthroughs have been made, substantial translational gaps persist between proof of concept in the laboratory and clinical implementation. This is driven by outstanding challenges in vascularization, immunological compatibility and spatiotemporal coordination of scaffold degradation with tissue neogenesis.

1.2. Research Questions

This review considers three research questions: RQ1: What is the mechanism of cell-scaffold interactions and how can scaffold carriers influence the cellular processes of adhesion, proliferation and differentiation required for tissue repair? How do the qualities of scaffold material impact the mechanisms? RQ2: What is the research base for the efficacy of scaffold carriers in bone and cartilage, skin and soft tissue and neural tissue restoration and which scaffold design parameters are most closely linked to beneficial regenerative results in each tissue system? RQ3: What are the major design problems limiting the clinical translation of scaffold carriers and which emerging smart scaffold techniques offer the most promising solutions?

2. THEORETICAL FRAMEWORK

2.1. ECM Biomimicry as the Design Principle of Scaffold Carriers

The extracellular matrix is a 3D network of fibrous structural proteins, glycoproteins and proteoglycans that surrounds and supports cells in native tissue [ ]. It offers mechanical support and 3D architectural structure for cell attachment and spatial patterning, and is a reservoir and signal transduction platform for growth factors, cytokines and matrix bound ligands that govern cell survival, proliferation and differentiation. The structural and metabolic complexity of ECM has been shown to facilitate cellular infiltration, vascularization, and functional tissue regeneration of decellularized natural tissues in ECM-based bioscaffolds. A review of ECM-derived materials for tissue engineering demonstrated that decellularized ECM scaffolds retain tissue-specific architecture, growth-factor binding capacity, and cell-instructive biochemical cues directing site-specific tissue regeneration, and that composite synthetic-natural scaffold systems are increasingly being designed to mimic these properties [1].

The main structural parameters of the ECM that need to be mimicked in scaffold design are the fibre architecture at the nano-to-micron scale (which controls cell alignment and mechanosensing), the pore geometry and interconnectivity (which affects the depth of cell infiltration and the efficiency of nutrient-waste transport), and the surface biochemistry (which controls the binding of integrins to ligands and activation of downstream signalling cascades). These characteristics define the materials engineering objective of contemporary tissue engineering, translated into realistic scaffold construction technologies such as electrospinning, freeze-drying, 3D bioprinting and hydrogel crosslinking [2].

2.2. Scaffold Material Classification and Design Rationale

The carrier materials of the scaffold are divided into three primary categories, natural biomaterials, synthetic polymers and composite systems. Natural biomaterials like collagen, gelatin, chitosan, hyaluronic acid, and fibrin closely mimic ECM biochemistry and present native cell-instructive signals through integrin-binding domains but generally exhibit low mechanical strength and variable degradation rates which limit their application in load-bearing tissue engineering applications. Synthetic polymers such as poly (lactic acid) (PLA), poly (glycolic acid) (PGA), poly (lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) provide superior mechanical tunability and well controlled degradation kinetics but lack the biological signalling richness of natural materials, and

often require surface functionalisation to promote adequate cell adhesion. The most commonly used design technique is the construction of composite scaffold systems, either by combining natural and synthetic components or by introducing bioactive inorganic phases such as hydroxyapatite (HA). These solutions combine the mechanical robustness and degradation control of synthetic polymers with the bioactivity and cell instructive features of natural ECM components. A systematic review of hydroxyapatite based scaffolds for bone tissue regeneration show that HA-polymer composite scaffolds have better osteoconductive and mechanical properties than single material systems and 3D printed composite constructs achieve geometry specific bone defect repair in both in vitro and in vivo models [3].

2.3. Cell-Scaffold Interaction Mechanisms

The cell's response to scaffold carriers is mediated by a hierarchy of molecular recognition, mechanical signalling, and transcriptional regulation which together decide whether the scaffold microenvironment supports or hinders successful tissue healing. The main molecular mechanism is cell attachment through integrins. Membrane spanning integrin receptors detect ligands from the ECM such as the arginine-glycine-aspartate (RGD) peptide sequence of fibronectin, vitronectin and collagen. Ligand binding triggers integrin clustering and recruitment of scaffold proteins such talin, vinculin, and focal adhesion kinase (FAK) to create focal adhesion complexes. FAK activation activates downstream mechanotransduction signalling pathways including RhoA/ROCK, PI3K/Akt and MAPK/ERK pathways which transduce the mechanical and biochemical properties of the scaffold into changes in gene expression to regulate cell survival, proliferation and lineage differentiation. The key mediators of mechanotransduction are integrin signalling and associated proteins that connect scaffold stiffness, topography and surface chemistry to cell fate decisions [4]. Especially, the stiffness of scaffold is significant. Engler et al. demonstrated that mesenchymal stem cells differentiate into neurogenic (0.1–1 kPa), myogenic (8–17 kPa) or osteogenic (25–40 kPa) lineages solely due to the stiffness of the matrix, offering the mechanobiological rationale for stiffness-tuned scaffold design [5].

3. SCAFFOLD EFFECTS ACROSS TISSUE SYSTEMS

3.1. Bone and Cartilage Tissue Repair

The most advanced clinical use of scaffold carrier technology is bone tissue engineering. This is related to the high incidence of significant bone abnormalities caused by trauma, tumour excision and congenital deformity. Hydroxyapatite-based composite scaffolds, i.e., collagen-HA and polymer-HA scaffolds have shown continuous efficacy in preclinical and clinical studies of bone defect repair. The HA phase osteoconductivity allows the adhesion and ingrowth of bone cells and the osteoinductive signals through the release of calcium and phosphate ions that induce alkaline phosphatase expression and mineralisation cascades in osteoblast precursors. In a study of collagen-based scaffolds with hydroxyapatite, the composite constructs seeded with differentiated bone marrow stromal cells showed excellent cartilage defect repair in vivo; histological analysis showed hyaline cartilage regeneration, territorial matrix deposition, and integration with the surrounding native cartilage tissue [6]. Three-dimensional bioprinting has dramatically advanced the fabrication of bone scaffolds, offering patient-specific geometries, graded porosity, and controlled deposition of several materials, which are particularly useful for repairing vast and complex bone defects [3].

Articular cartilage is avascular, aneural and has a very low intrinsic repair capacity posing unique challenges for cartilage engineering. The zonal organization of articular cartilage into superficial, transitional and deep zones with differing collagen orientations and mechanical properties has guided the creation of multi-layer gradient scaffolds to promote zone-specific chondrogenic growth [6].

3.2. Skin and Soft Tissue Repair

Skin wound healing is a carefully orchestrated sequence of haemostasis, inflammation, proliferation and remodelling stages, disruption of which results in chronic non-healing wounds with significant clinical morbidity. Scaffold carriers perform multiple functions at the same time in skin wound healing such as providing a provisional matrix for fibroblast migration and keratinocyte re-epithelialisation, maintaining wound moisture balance, delivering growth factors and antimicrobial agents and modulating the wound inflammatory microenvironment. We report a multifunctional bilayer electrospun nanofiber/hydrogel scaffold consisting of a chitosan/gelatin nanofiber layer and a drug-loaded hydrogel layer that mimics epidermal-dermal architecture to achieve ~97% wound closure in scratch test animals. The composite construction exhibited ~45% higher tensile strength, 93% antioxidant activity and extremely strong antibacterial efficacy against gram-positive and gram-negative pathogens [7]. A further advanced technique for the use of endogenous bioelectric signals in wound healing is electroactive electrospun nanofibrous scaffolds with conductive polymers or piezoelectric materials. Electrical stimulation of the scaffold results in increased keratinocyte migration, fibroblast proliferation and angiogenesis leading to faster healing and improved tissue architecture in acute and diabetic wound models [8].

3.3. Neural Tissue Repair

The most problematic aspect of scaffold design for peripheral nerve injury restoration is the demanding structural, mechanical and electrochemical requirements for axonal guidance over damage gaps, Schwann cell migration, myelination support and electrical signal conduction. Nerve guidance conduits (NGCs) are tubular scaffold structures that span nerve defect gaps and offer a supportive milieu for axonal regrowth. The present scaffold carrier construction for peripheral nerve rehabilitation using a number of synthetic polymer (PLGA, PCL) and natural material (collagen) conduits clinically authorised for gaps of up to ~30 mm. According to a systematic review of scaffold design for peripheral nerve regeneration, the efficacy of NGCs depends on the integrated optimisation of material selection, luminal architecture (e.g. multi-channel configurations and aligned nanofiber fillings), surface functionalisation with neural adhesion molecules and controlled release of neurotrophic factors such as NGF, BDNF and GDNF [9]. In clinical studies, PLGA conduits have been associated with functional recovery within 3–6 months of implantation in tissue engineering approaches for peripheral nerve repair based on biomaterials, while next-generation conductive and piezoelectric conduit designs have demonstrated enhanced axonal regeneration outcomes in preclinical models by providing electrical stimulation that mimics the endogenous bioelectric microenvironment of native nerve tissue [10].

4. KEY DESIGN CHALLENGES IN SCAFFOLD CARRIER DEVELOPMENT

4.1. Vascularisation, Immunogenicity, and Degradation Kinetics

The main obstacles to the clinical translation of scaffold carrier systems for tissue restoration are three interconnected design problems. First, the vascularization deficit. Thick scaffold constructs (beyond 200 μm from the nearest capillary) cannot provide sufficient oxygen and nutrient supply to the scaffold core to keep the cells alive. This problem persists despite the significant progress in prevascularization strategies, pro-angiogenic growth factor delivery, and endothelial cell co-cultures. Second, the immunogenicity of scaffold materials, particularly those derived from natural animal sources, is the propensity to stimulate host immune responses that result in chronic inflammation and foreign body reactions, leading to encapsulation of the scaffold and loss of function. This difficulty demands careful attention to decellularisation procedures, endotoxin removal and material

biocompatibility testing in both innate and adaptive immune pathways. Third, degradation kinetics mismatch implies that the degradation rate of the scaffold and the rate of new tissue formation are not synchronised in time and can result in either premature mechanical failure (when degradation is faster than tissue formation) or a persistent foreign body that hinders the organization of mature tissue (when degradation is slower). The review of bioengineered scaffolds and smart biomaterials confirms that the challenges of clinical translation, such as immune compatibility, vascularization deficits, mechanical mismatch, and biodegradation control, all require a unified assessment framework for long-term efficacy and safety evaluation [11].

5. DISCUSSION: SMART SCAFFOLDS AND FUTURE DIRECTIONS

The most promising strategy to bridge the gap between the static properties of conventional scaffold materials and the dynamic, responsive nature of the native ECM is the emergence of stimulus-responsive smart scaffolds, constructs whose structural, mechanical or biochemical properties dynamically change in response to physiological cues such as pH, temperature, enzymatic activity or mechanical loading. In the context of bone tissue engineering, smart scaffolds demonstrate that stimuli-responsive 3D-printed constructs can induce tailored therapeutic responses (e.g., antibacterial activity, growth factor release, and stiffness modulation) in response to specific conditions of the wound microenvironment, achieving functional outcomes that static scaffolds are unable to [12]. In response to RQ1, cell-scaffold contact is largely regulated by integrin-FAK-mechanotransduction pathways and cell destiny outcomes are decided by scaffold stiffness, surface chemistry and topography in concert. To answer RQ2: The most-supported scaffold designs in terms of evidence in each specific tissue system are HA-composite scaffolds for bone, bilayer nanofiber-hydrogel systems for skin and multi-channel conductive conduits for peripheral nerve. Answering RQ3: Vascularization, immunogenicity and degradation mismatch are the key translational barriers and smart stimulus-responsive scaffolds present the most promising framework to address these limitations by dynamic ECM mimicry.

6. CONCLUSION

Scaffold carriers have been found as important facilitators of tissue repair and rehabilitation in systems of bone and cartilage, skin and soft tissue, and brain tissue. The efficacy is determined by synergistic optimisation of the material composition, architectural design, surface chemistry and degradation kinetics for the specific cellular milieu of each target tissue. A solid scientific foundation for the rational design of next generation scaffold systems is provided by the molecular basis of scaffold carrier function, including ECM biomimicry, integrin-mediated mechanotransduction and stiffness-guided lineage differentiation. The current frontier of design solutions are stimulus-responsive smart scaffold systems which are needed because to the continuous translational difficulties of vascularization, immunogenicity and mismatch of degradation kinetics that require more materials science and bioengineering innovation. Nevertheless, practical use of scaffold carriers for regeneration requires not just innovations in materials but also standardised preclinical-to-clinical translation frameworks that can reliably predict functional outcomes within the whole complexity of cells in vivo.

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