

Overcoming Vascularization Barriers in Tissue Engineering: Roles of Nanomaterials, Immunomodulation, and Biofabrication

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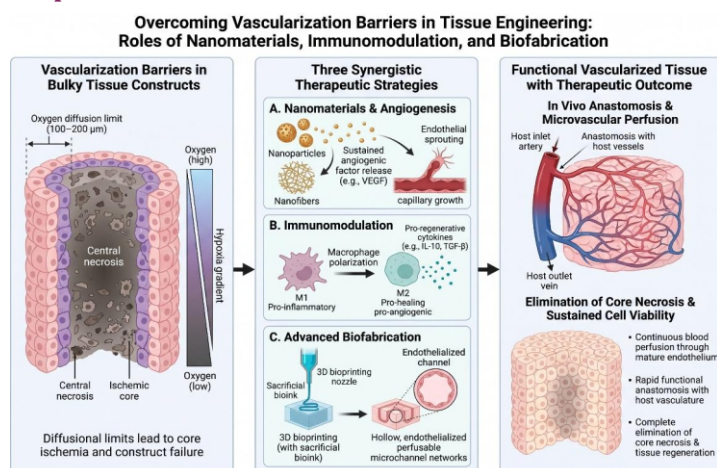
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ABSTRACT

The goal of tissue engineering is to replace, regenerate, or restore damaged tissues by combining cells, biomaterials, and bioactive cues cooperatively. The practical translation of engineered tissues is still constrained by insufficient vascularization, immune-mediated inflammation, and inadequate structural and functional integration, despite notable advancements in scaffold design, stem cell biology, and biofabrication technologies. With a focus on the functions of stem cell sources, such as induced pluripotent stem cells, embryonic stem cells, and mesenchymal stem cells, as well as developments in biomaterial scaffold design, this review offers a thorough overview of the history and fundamental ideas of tissue engineering. The benefits and translational challenges of *in vitro*, *ex vivo*, and *in vivo* scaffold techniques are given special attention. This review examines the development of nano-enabled biomaterials as practical ways to get beyond diffusion restrictions and encourage angiogenesis, and it emphasizes vascularization as a crucial bottleneck in engineered tissues. As next-generation regeneration approaches, recent advances in immunomodulatory nanomaterials that control macrophage polarization and connect inflammation with vascular expansion are investigated. Additionally, the combination of nanotechnology and cutting-edge biofabrication techniques, such as 3D bioprinting and microfluidics, is investigated as a potent way to produce architecturally intricate, functional, and perfusable tissue constructs. In order to expedite the clinical translation of tissue-engineered therapies, future directions are finally discussed, with a focus on multifunctional nano-engineered platforms that combine angiogenic, immunomodulatory, and biofabrication capabilities.

Keywords: Biomaterial scaffolds, vascularization, tissue engineering, nanotechnology, and immunomodulation.

Graphical Abstract



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1. Introduction

We know that tissue engineering is the development of artificial organ and tissue systems; however, the above statement warrants explanation. Organ growth using mechanical components is an advanced science that has been practiced for some time, and mechanical hearts and left ventricular assist devices have already been used in patients. Tissue engineering must be differentiated from this field of study because its aim is to produce biological artificial organs which appear and function as mammalian organs. Cells and biomaterials (which replicate the mammalian extracellular matrix) are essential elements of artificial organs produced using tissue engineering methods [1]. Tissue engineering is a converging discipline that integrates fundamental concepts in biology, materials science, and engineering to restore, maintain, or enhance tissue function.

The prime aim is the development of biological substitutes for injured or defective organs and tissues. The method normally involves three significant elements. New tissue development is dependent on the availability of stem cells, progenitor cells, and differentiated cells. Scaffolds refer to biocompatible tissue structures (natural or synthetic) composed of a three-dimensional framework for cell development and tissue formation. Growth factors, cytokines, and mechanical or chemical stimuli are all bioactive molecules that control tissue development, cell differentiation, and proliferation [2]. Tissue engineering has many applications, including skin for victims of burns, artificial cartilage, bone growth, vascular grafts, and even complex organ fabrication. Advancements in 3D bioprinting, stem cell engineering, and biomaterials have spurred development in the subject matter so that it is rapidly approaching clinical use [3].

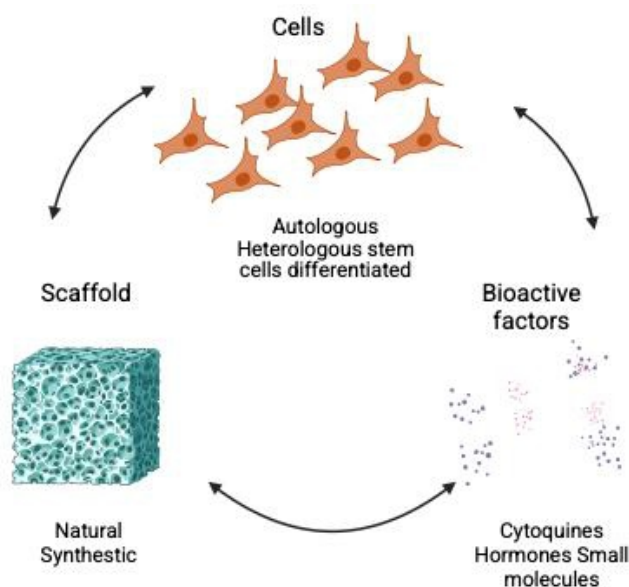


Figure1: The "triad" of tissue engineering [4]

1.1 Origin of tissue engineering

Across the history of humankind, artificial construction of tissue, organs, and even more advanced biological entities has been a fantasy and myth. The idea turned into an actuality a few decades back, but it has just recently been applied to clinical practice. Regenerative medicine and tissue engineering are terms employed to establish the field of biomedicine that is concerned with turning these basic ideas into useful approaches. Various aspects of making new tissues and organs from small pieces of living samples have been solved in the scientific community, but it is unclear how strongly the new approaches will influence clinical practice in the future. To this extent, it seems that it is mandatory to recapitulate where the visions and attempts started to foresee or predict where tissue engineering and regenerative medicine would develop. An abundance of representations in literature and the arts reflects the human aspiration to be able to create living beings in themselves or at least portions of beings. The imagined steps to generate life are determined by the social, cultural, and scientific environment of individuals at that moment. The [figure 2] famous painting "Healing of Justinian" a representation of the legend of St. Cosmas and St. Damien (278 AD) showing the transplantation of a homograft limb on a wounded soldier, is one of the early representations of the vision of regenerative medicine [5].

As the human being advanced in the knowledge of nature and as they acquired more refined culture methods, they dreamed of creating living organisms through the use of physicochemical or biological methods. During the Middle Ages and Renaissance in Europe, several scientists believed that alchemy could create living organisms [5].



Figure 2: Healing of Justinian [5]

The phrase "tissue engineering" was coined in the late twentieth century, yet the work dates way back. Surgeons attempted skin grafts and cartilage transplants that would lead to regenerative medicine in the early 1900s. Cell culture methods invented between the 1950s and the 1960s pushed science to its first strides, enabling scientists to cultivate and sustain mammalian cells in the laboratory. These noteworthy advances opened the door to the incorporation of living cells into synthetic scaffolds. The discipline achieved formal establishment in 1993, when Langer and Vacanti wrote their seminal paper in *Science*, where tissue engineering was defined as "an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function" [6]. This publication set the conceptual foundations of contemporary TE, with emphasis on the three crucial components: cells, scaffolds, and signaling molecules. During the following decades, major milestones have been the creation of biodegradable polymer scaffolds, the establishment of stem cell biology, and the advent of bioreactors that could simulate physiological conditions.

During the 2000s, enhanced capabilities from biomaterials, reprogramming of stem cells (iPSCs, 2006), and nanotechnology further expanded the capabilities of TE. Still more recently, the most recent advances in 3D bioprinting, organoids, and organ-on-a-chip technologies have transformed the landscape, making the dream of functional tissue and organ replacement nearer to clinical reality [7]. Today, TE is seen as a pillar of regenerative medicine with potential uses from engineered skin and cartilage to new constructs for heart, liver, and nerve tissue. The journey has been incremental, however, from the early non-sophisticated grafting methods to highly advanced, patient-specific, and translation-focused methods [8].

1.2 Overview of Tissue Engineering

The creation of synthetic or semisynthetic tissue that can be used instead of human tissue in surgery or research. Different kinds of tissue have been developed and are currently being researched, including skin, bone, cartilage, cornea, and spinal tissue, using various combinations of biopolymers, cultured cells, and growth factors. For example, the first such product to gain approval for clinical use was a form of artificial skin consisting of a thin sheet of collagen gel infiltrated with two layers of cultured human cells known as keratinocytes on the outer surface to form the epidermis and fibroblasts on the inner surface to form the dermis. More rigid tissues such as synthetic bone and cartilage are typically based on a biopolymer scaffold, which is seeded with cultured bone cells or cartilage cells to secrete the natural tissue material [9]. The scaffold can be inserted *in situ*, for example at a fracture site, or used to construct a new body part entirely *in vitro*. For successful colonization and growth by cultured cells or the body's own cells, the scaffold is treated with appropriate growth factors [10]. For example, bone cells require a substance called bone morphogenetic protein. Another strategy is the manipulation of stem cells in three-dimensional cultures by sequentially exposing them to a suite of signaling molecules (morphogens) that mimic the factors determining their development into a particular tissue or organ in the body. Tissue engineering requires detailed knowledge of cell culture techniques, biomolecules, and the biochemical properties of natural tissues. Figure 3 illustrates the working definition of tissue engineering, which encompasses the principles that have evolved in the field of tissue engineering.

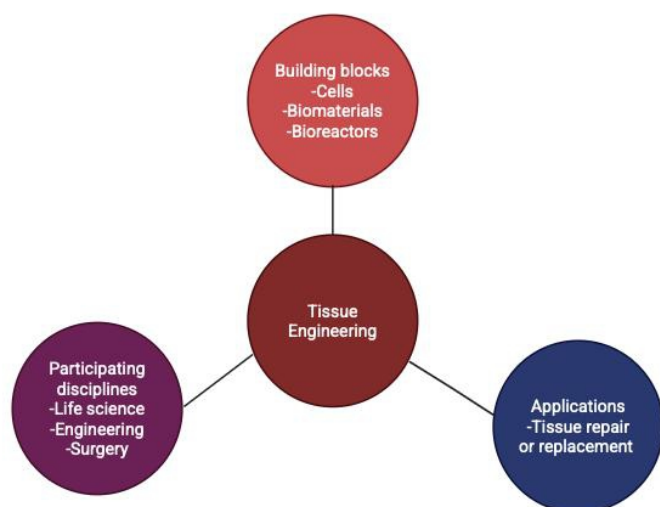


Figure 3: Definition of Tissue Engineering [11]

Tissue engineering is a multidisciplinary field bringing together experts from engineering, life sciences and medicine, utilizing the building blocks of cells, biomaterials and bioreactors for the development of 3-dimensional artificial tissue and organs which can be used to augment, repair and/or replace damaged and/or diseased tissue [11]. This definition illustrates the multidisciplinary nature of tissue engineering.

2. Role of stem cells in tissue engineering

2.1 Induced Pluripotent stem cells

Induced pluripotent stem cells (iPSCs) have emerged as a transformative tool in tissue engineering, offering a renewable and patient-specific source of cells for skeletal muscle regeneration [12]. Unlike satellite cells, which are limited in number and difficult to isolate, iPSCs possess pluripotency and self-renewal capacity, allowing differentiation into various lineages, including myogenic progenitor cells. Derived from somatic cells such as fibroblasts, peripheral blood mononuclear cells, or urinary epithelial cells, iPSCs overcome ethical and immunological barriers associated with embryonic stem cells, making them ideal for personalized regenerative therapies [13]. The reprogramming of somatic cells into iPSCs is achieved through Yamanaka factors (Oct4, Sox2, Klf4, and c-Myc), using either viral methods like retroviral and lentiviral transduction, which are highly efficient but may induce mutagenesis, or safer non-viral approaches employing plasmid DNA, mRNA, miRNA, or small molecules such as valproic acid and BIX-01294 [14]. Optimized culture systems, including feeder-free conditions and 3D bioreactors, further enhance iPSC proliferation and differentiation potential.

For skeletal muscle engineering, iPSCs are directed toward the myogenic lineage using either gene-based or small-molecule-based approaches. Gene-based strategies involve the expression of transcription factors such as Pax-7 or Pax-3 to activate myogenic programs, while chemical induction utilizes signaling molecules like CHIR99021 and LDN193189 to modulate Wnt and BMP pathways, producing Pax7⁺ progenitors that mature into myosin heavy chain (MHC)-expressing myotubes [15,16]. Recent advances in 3D tissue culture systems and scaffold-based constructs have enabled the formation of functional iPSC-derived muscle tissues that mimic native architecture, promote myofiber alignment, and establish neuromuscular junctions [17]. These 3D models have proven valuable for disease modeling, drug screening, and regenerative therapy, effectively replicating conditions such as Duchenne muscular dystrophy, limb-girdle muscular dystrophy, and amyotrophic lateral sclerosis [18,19]. Furthermore, iPSC-derived muscle tissues are being integrated into biohybrid systems for soft robotics and bioactuators, where they are combined with materials like polydimethylsiloxane (PDMS) or electrospun nanofibers to generate contractile forces for movement and neural interfacing [20]. Despite major advances, challenges persist, including incomplete maturation, heterogeneous cell populations, potential teratoma formation, high production costs, and scalability limitations. Ongoing research focuses on optimizing differentiation efficiency, improving maturation through biophysical stimulation, standardizing large-scale production, and enhancing integration with biomimetic materials. Overall, iPSCs hold great promise for developing functional skeletal muscle tissues with broad applications in regenerative medicine, personalized therapy, drug discovery, and biohybrid robotics [21].

2.2 Embryonic Stem Cells

Human embryonic stem cells (hESCs) have long been recognized as a unique and powerful cell source for regenerative medicine because of their pluripotent nature and capacity for unlimited self-renewal. Derived from the inner cell mass of blastocysts, these cells can differentiate into any somatic cell type, making them ideal candidates for generating replacement tissues and organs [22]. The hESCs provide an excellent in vitro model for studying early human development, lineage commitment, and differentiation processes. Their ability to form specific cell types such as cardiomyocytes, hepatocytes, pancreatic β -cells, and neural cells demonstrates their potential in repairing or replacing tissues affected by degenerative diseases, including diabetes, myocardial infarction, liver disorders, and neurodegenerative conditions. Moreover, hESCs are invaluable for testing drug efficacy and toxicity in human-specific cellular contexts. However, there are several obstacles in the clinical application of hESCs, notably ethical concerns surrounding embryo destruction, the possibility of immune rejection after transplantation, and the risk of teratoma formation due to incomplete differentiation, the hESCs remain the gold standard for pluripotent stem cell research, providing critical insights into developmental biology and serving as the foundation upon which regenerative medicine continues to advance toward clinical translation.

2.3 Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent stromal cells with remarkable capacity for self-renewal and differentiation into mesodermal lineages such as osteoblasts, chondrocytes, and adipocytes, making them a cornerstone of tissue engineering and regenerative medicine [23].

MSCs can be isolated from diverse sources, including bone marrow, adipose tissue, umbilical cord, dental pulp, placenta, and amniotic fluid, each offering unique biological properties and regenerative potential. Bone marrow-derived MSCs (BM-MSCs) remain the most extensively characterized, but their invasive harvesting and declining yield with donor age have driven the exploration of alternative sources. Adipose-derived MSCs (AD-MSCs) are abundant, easily accessible, and exhibit strong proliferative ability [24], while umbilical cord-derived MSCs (UC-MSCs) and amniotic MSCs display lower immunogenicity and greater expansion potential, making them promising for allogeneic therapies. MSCs contribute to tissue repair not only through direct differentiation but also via paracrine signaling, secreting growth factors, cytokines, and extracellular vesicles that modulate inflammation, angiogenesis, and immune responses. These immunomodulatory and trophic properties enable MSCs to promote regeneration in musculoskeletal, cardiovascular, hepatic, neural, and dermal tissues. Integration of MSCs with biomaterial scaffolds such as hydrogels, collagen matrices, and bioactive polymers enhances cell survival, differentiation, and tissue-specific functionality. Advances in 3D bioprinting and nanotechnology have further improved MSC delivery and spatial organization within engineered constructs [25]. However, challenges remain regarding donor variability, senescence during expansion, potential tumorigenicity, and inconsistent differentiation outcomes. The future directions in MSC-based tissue engineering should focus on standardizing isolation and characterization protocols, optimizing scaffold cell interactions, and employing genetic or biochemical preconditioning to enhance regenerative efficacy. MSCs represent a versatile and clinically relevant cell population that bridges basic stem cell biology with translational applications in tissue repair and regeneration [26].

Table 1: Comparison between Autologous, Allogenic and Xenogeneic cells

Characteristics	Autologous cells	Allogenic cells	Xenogenic cells
Origin	Cells harvested and reinfused from the same individual.	Cells derived from a donor of the same species (genetically distinct individual).	Cells taken from a different species (Animal to Human).
Immunogenicity	Very low risk of immune rejection because cells are self [27].	Moderate risk. It requires HLA mapping or immunosuppression. Immune modulation strategies are increasingly studied.	Very high immune barrier. Xenograft rejection (hyperacute, acute, chronic) remains major challenge [28].
Ethical and regulatory considerations	Lower regulatory complexity, fewer ethical donor issues.	Higher complexity than autologous. Requires donor consent, cell banking, regulatory oversight [29].	Highest complexity, cross species ethics, zoonotic risk, genogenic antigen issues. [30]
Availability	Limited by patient's health, time required for harvesting and expansion [31].	Greater scalability: Donor derived off the shelf options, cell banks [32].	Potentially very high supply (animal sources) but translation and safety limit real world use [33]
Processing time and logistics	Longer lead time: isolation, expansion, patient-specific processing [34]	Donor cells prepared and stored for immediate use [35]	May require further modification or immuno engineering, increasing complexity [36]
Clinical applications examples	Personalized therapies: autologous stem cell injection, iPSC derived autologous therapies.	Donor stem cell transplantation (hematopoietic stem cells, allogeneic MSCs), "off the shelf" regenerative therapies [37].	Experimental organ and tissue xenotransplants, xenogenic scaffolds, Preclinical models [38].
Advantages	Immune compatible, Personalized, fewer ethical donor concerns.	Availability, standardization, ready for acute interventions.	Large supply, potential to overcome human donor shortages, novel platforms.
Limitations	Patient's cell quality may be poor (age, disease), time consuming and expensive.	Immune rejection risk, donor recipient mismatch issues, immunosuppression side effects.	Major immune rejection, zoonosis risk, species barrier, regular or ethical hurdles.

3. Biomaterials and scaffolds in Tissue engineering

3.1 Advances in biomaterials scaffold design for tissue engineering and regenerative medicine

Biomaterials and scaffolds form the structural and functional foundation of tissue engineering and regenerative medicine, enabling the creation of viable tissue constructs that mimic native physiological environments [39]. Over the past three decades, advancements in tissue engineering and regenerative medicine have expanded the repertoire of biomaterials, fabrication strategies [40], and cellular approaches for tissue regeneration and disease modeling.

Biomaterials serve as three-dimensional frameworks that support cell adhesion, proliferation, differentiation, and extracellular matrix (ECM) deposition while maintaining biocompatibility and controlled biodegradability. Modern research emphasizes the design of functionalized polymers decorated with bioactive moieties such as RGD peptides, laminin-mimetic sequences, and MMP-sensitive sites to enhance biomimicry and cellular responses [41,42]. Concurrently, technological innovations such as electrospinning, 3D bioprinting, and microfluidic fabrication have revolutionized scaffold design by improving precision, porosity, and mechanical stability [43]. ECM-based biomaterials derived through tissue decellularization offer native-like environments conducive to cell maturation and integration, while emerging models like organoids provide self-assembling, physiologically relevant systems for studying development and pathology [44]. Despite these advancements, clinical translation remains hindered by challenges including inadequate vascularization, poor tissue interface integration, limited cell density and maturation, and uncontrolled immune responses to implanted scaffolds [45,46]. Addressing these issues requires the development of immunomodulatory biomaterials capable of guiding macrophage activity and promoting angiogenesis [47]. Overall, the evolution of biomaterial science continues to drive innovation in tissue engineering and regenerative medicine, bridging the gap between laboratory discoveries and clinically viable tissue-engineered therapies [48].

3.2 *In vivo*, *Ex vivo* and *In vitro* scaffolds

By directly implanting biomaterial constructs into living organisms, *in vivo* scaffold techniques enable tissue regeneration by utilizing host biological processes [49]. Following implantation, these scaffolds are intended to facilitate cell adhesion, recruitment, and host-driven vascular ingrowth, allowing the development of functional tissue within the physiological milieu [50]. Novel bioengineered grafts that self-assemble inside host systems have been highlighted in recent research [51]. For example, scaffold-guided tubular vascular tissues generated in rat models show enhanced morphogenesis and integration without requiring substantial *in vitro* preparation. This method supports structural remodeling and the restoration of healthy blood flow by taking advantage of the natural regeneration cues of the *in vivo* niche to promote ordered tissue development around and inside the scaffold [52]. In order to match the rate of new tissue development and encourage prolonged vascularization, *in vivo* scaffolds are increasingly designed for biocompatibility, mechanical resilience, and controlled breakdown kinetics [53]. For instance, subcutaneously implanted composite 3D-printed scaffolds show distinct patterns of degradation and macrophage-mediated tissue remodeling that impact angiogenic signaling and host integration over time [54].

These investigations highlight the significance of host responses in scaffold performance [55], where angiogenesis and extracellular matrix deposition surrounding *in vivo* implants are influenced by both pro- and anti-inflammatory macrophage activities [56].

Ex vivo scaffold techniques, on the other hand, concentrate on creating and developing tissue constructs outside of the body prior to implantation. These techniques frequently entail seeding cells onto scaffolds in a regulated setting that promotes tissue organization and the development of pre-vascular networks [57]. The use of decellularized tissue scaffolds for organ engineering, in which the original extracellular matrix architecture is maintained to direct cellular infiltration and vascular patterning in *ex vivo* cultures, is a well-known example [58]. Decellularized matrices lower immunological responses, offer natural biochemical cues, and promote host anastomosis following implantation. The most recent reviews highlight the potential for creating intricate, pre-organized vascular networks that closely resemble natural tissue architecture through the use of such decellularized scaffolds in organ-level *ex vivo* engineering [59]. *Ex vivo* techniques provide more control over microarchitecture, cell composition, and perfusable vessel development before implantation, whereas *in vivo* scaffolds depend on host biology for vascularization and remodeling [60, 61]. In an effort to address the drawbacks of each strategy alone, hybrid approaches that combine *ex vivo* pre-vascularization with later *in vivo* integration are becoming more popular [62]. These techniques aim to improve graft performance and speed up perfusion by creating vascular conduits and microvascular networks in scaffold structures *ex vivo* and then implanting them to interface with host circulation [63-65]. Recent *in vivo* and *ex vivo* research has led to advancements in scaffold design and fabrication, which collectively highlight a trend toward multiscale and biomimetic approaches that bridge physiological complexity and clinical viability in regenerative medicine [66-70]. Before transplantation or functional testing, *in vitro* scaffold platforms are engineered constructs that facilitate cell proliferation, differentiation, and tissue creation in a controlled laboratory setting [71]. *In vitro* systems offer exact control over biochemical, mechanical, and physical stimuli, allowing systematic research of cell-matrix interactions and pre-organization of tissue constructs, in contrast to *in vivo* scaffolds, which depend on host physiology [72]. In order to promote functional maturation and vascular network formation, recent developments concentrate on developing biomimetic scaffolds that mimic the original extracellular matrix (ECM) architecture and dynamic milieu of certain tissues [73, 74]. For instance, 3D nanofibrous scaffolds made by electrospinning have been extensively used to simulate networks of collagen and elastin fibers, directing stem cell differentiation and promoting endothelial tubulogenesis *in vitro*, which is essential for subsequent vascularization after implantation [75, 76]. Because of their adjustable mechanical characteristics and biochemical signals, nanocomposite hydrogels containing bioactive nanoparticles (such as bioactive glass and graphene derivatives) further improve cellular adhesion, proliferation, and lineage-specific differentiation [77].

In vitro prevascularization with co-culture systems of endothelial cells and mesenchymal stem cells that form capillary-like networks prior to *in vivo* transfer is made possible by recent research showing that scaffold stiffness, pore interconnectivity, and nanoscale topography significantly influence cell behavior [78].

The development of vascularized in vitro tissue models, where perfusable microchannels are integrated into scaffolds to support nutrient diffusion and simulate fluid shear stress, has also been made possible by advances in bioprinting and microfluidics [79-81]. This enhances the physiological relevance of engineered tissues for drug testing and disease modeling [82]. Additionally, the incorporation of dynamic culture methods like bioreactors, which use regulated fluid flow and mechanical stimulation, increases ECM deposition, encourages tissue maturation, and prepares structures for load-bearing applications like cartilage and bone [83]. All of these advancements point to a trend toward increasingly complex in vitro scaffolds that bridge the gap between bench and bedside in regenerative medicine by facilitating 3D tissue synthesis in the lab and acting as predictive models for in vivo performance [84-86].

4. Vascularization challenges in engineered tissues and the emergence of nano-based biomaterials strategies.

The insufficient development of functioning circulatory networks within the engineered tissue is one of the most enduring obstacles to transferring engineered tissue constructs to therapeutic applications [87]. Diffusion constraints cause hypoxia and necrosis in constructs thicker than ~100–200 µm, which results in cell death and poor integration after implantation [88]. Native tissues rely on hierarchical blood artery systems to deliver oxygen and nutrients and eliminate waste [89, 90]. In complicated tissues like bone, heart muscle, and vast soft tissues, where quick and coordinated vascular ingrowth is essential for life and functional performance, this difficulty is exacerbated [91]. Conventional angiogenic methods, including growth factor bolus administration or straightforward scaffold porosity, sometimes lead to inadequate or disordered vascularization, which restricts tissue integration and survival [92]. Nano-based biomaterial techniques have become effective tools to improve and direct vascularization within scaffolds in order to overcome these obstacles [93]. By imitating the geometry of the natural extracellular matrix (ECM), nanostructured materials can offer nanoscale cues that encourage endothelial cell adhesion, migration, and organization into networks resembling capillaries [94]. By promoting endothelial colonization and sprouting, it has been demonstrated that modifying scaffold physical characteristics at the nanoscale, such as pore size, surface roughness, and stiffness, can improve angiogenic responses [95-97]. In addition to physical cues, growth factor instability and burst release can be addressed by engineering nanomaterials to transmit pro-angiogenic signals in a controlled, continuous manner [98, 99]. For example, scaffolds with functional nanoparticles or nano-carriers can localize and sustain the release of factors like VEGF, improving vascular development while reducing off-target effects [100,101]. Additionally, multifunctional nano scaffold platforms have made it possible to integrate cell-based methods and provide biochemical signals in a spatiotemporal manner, facilitating the creation of pre-vascular networks prior to implantation [102-106]. The creation of VEGF-activated nanostructured scaffolds that produce pro-angiogenic microenvironments appropriate for chronic tissue regeneration and wound healing, exhibiting enhanced vessel density and functional results, is one example of recent advancements [107]. Similarly, it has been demonstrated that the nanoscale incorporation of bioactive ions (such as silicon, copper, and magnesium) in scaffold matrices stimulates angiogenesis and

endothelial activity, providing a bioinstructive approach to vascularization [108,109]. Together, these approaches mark a paradigm shift toward multifunctional, nano-enabled scaffolds that combine biological signaling and structural support to get over the vascularization bottleneck that has long hampered the translation of tissue engineering [110-112].

4.1 Immunomodulatory nanomaterials linking inflammation and vascularization

Nanomaterials designed for immunomodulation are now being used to bridge inflammation and vascularization, and a new study highlights the crucial function of the immune microenvironment in coordinating angiogenesis during tissue regeneration [113,114]. The distribution of growth factors and structural support were the main goals of traditional scaffold designs, but they frequently failed to take advantage of the immune system's inherent capacity to control vascular responses [115,116]. On the other hand, cleverly engineered nanomaterials have the ability to alter the behavior of immune cells, specifically influencing macrophage polarization toward a pro-regenerative (M2) phenotype, which is closely linked to increased pro-angiogenic cytokine secretion and better neovascularization within engineered tissues [117,118]. The potential of immunomodulatory nanomaterials to coordinate angiogenic signaling and inflammation resolution *in vivo* is highlighted by recent studies showing that multifunctional nanocomposite hydrogels can promote M2 polarization of macrophages, thereby reducing chronic inflammation at defect sites while simultaneously promoting vascularized bone regeneration [119,120]. An actively controlling the macrophage phenotype (M1 → M2), immunomodulatory nanomaterials improve vascularization in engineered tissues by lowering chronic inflammation and increasing angiogenic factor release [121]. By reprogramming immune metabolic states and signaling pathways, nanomaterials can provide pro-angiogenic microenvironments that are essential for tissue regeneration [122]. An important next-generation tactic for vascularized tissue engineering is the integration of immunomodulatory and angiogenic activities in nanocomposite scaffolds [123].

5. Integration of nanotechnology with advanced biofabrication

In order to overcome long-standing issues like restricted nutrient diffusion, mechanical inadequacy, and the structural complexity of engineered constructs, the integration of nanotechnology with cutting-edge biofabrication techniques has emerged as a crucial tactic in the engineering of vascularized and functional tissues [124]. The addition of nanoparticles to bioinks and scaffolds for 3D bioprinting, which improves mechanical characteristics, cell-matrix interactions, and biological signal transduction, has been a significant advancement [125,126]. In addition to offering localized biochemical cues that direct angiogenesis and tissue formation, nanomaterials such as nanoparticles, nanofibers, and nano-reinforced hydrogels have been demonstrated to enhance print fidelity, scaffold integrity, and cellular viability both during and after bioprinting [127,128]. These nanobioinks improve vascular sprouting and network development in vitro and in vivo by making it easier to create intricate geometries and hierarchical microstructures that closely resemble the architecture of the natural extracellular matrix. For instance, mechanically strong, extremely porous scaffolds that promote stem cell proliferation and endothelial alignment for early

vascular development have been made possible by integrating nanomaterials with molten electro writing and extrusion-based bioprinting [129]. During 3D bioprinting, nanomaterials in bioinks improve biological responses and mechanical characteristics. Complex designs are supported by nano-reinforced scaffolds, which further enhance print stability and resolution. Pre-vascularized and perfusable constructions are made possible by the integration of nanotechnology with microfluidic and computational biofabrication [130].

5. Future Directions

New developments in biomaterials combine angiogenic and immunomodulatory properties into a single platform; multifunctional composite scaffolds with specific immunoregulatory characteristics have been created that actively promote capillary formation and endothelial recruitment in addition to suppressing excessive inflammatory responses [131-135]. When compared to traditional scaffolds, a polymeric composite scaffold with intrinsic immunomodulatory and pro-angiogenic characteristics achieved better functional results in vascularized bone regeneration, according to a typical 2025 study [136-140]. When taken as a whole, these new developments show a paradigm change in tissue engineering, where nanomaterials are deliberately designed to mediate the interaction between vascularization and inflammation. Researchers are now able to overcome a significant obstacle in clinical translation by creating regenerative microenvironments that more successfully support angiogenesis and functional tissue integration by fine-tuning immune responses through nanoscale design [141-145]. In addition to improving structural and functional results, recent research highlights how this synergy between nanotechnology and biofabrication enables customized control over porosity, stiffness, and bioactivity at various length scales—a crucial prerequisite for effective tissue integration [146,147]. The creation of perfusable microvascular networks within engineered constructions has been made possible by concurrent developments in microfluidic biofabrication and computational design directed by nanoscale cues, which hold great promise for organ-scale tissue engineering [148,149]. Despite these developments, there are still issues with large-scale manufacturability, biocompatibility, and uniform nanomaterial dispersion, all of which are current research topics targeted at converting nano-enabled biofabrication into clinical applications [150].

6. Conclusion

With the goal of creating viable tissue replacements, tissue engineering has developed into a highly interdisciplinary area that integrates stem cell biology, biomaterials science, and advanced biofabrication. The structural and biological fidelity of synthetic tissues has been greatly enhanced by developments in scaffold design and fabrication as well as advances in stem cell technology, especially iPSCs and MSCs. However, insufficient vascularization continues to be a significant obstacle to clinical translation, particularly for complicated and big constructions. By offering biomimetic physical cues, regulated angiogenic signaling, and immunomodulatory functionalities that together support vascular network creation and host integration, recent nano-enabled biomaterial techniques present intriguing answers.

The production of functional and perfusable constructs is accelerated by the precise control over tissue architecture and microenvironmental cues made possible by the confluence of nanotechnology with 3D bioprinting, microfluidics, and bioreactor systems. The next generation of clinically feasible tissue-engineered treatments is anticipated to be driven by the ongoing integration of immunomodulatory nanomaterials with sophisticated biofabrication technologies, notwithstanding ongoing difficulties with scalability, safety, and regulatory translation.

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