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Review Article

A review on scaffolds: A medical marvel

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ABSTRACT

The increasing need for organ replacements in an aging society and the loss of tissues and organs due to diseases, accidents, and congenital anomalies are driving the development of new techniques such as three-dimensional bioprinting, precision extrusion deposition, bio-fabrication, elective laser sintering, nanocoating, supramolecular materials, stereolithography, induced pluripotent stem cells, and organoids, fused deposition modelling, electrospinning, and three-dimensional printing for tissue engineering and regenerative medicine. The creation of a wide range of materials, including natural and synthetic polymeric scaffolding materials for therapeutic applications for the repair and regeneration of various deficits and deformities, has been made easier by recent advancements in production techniques and biological materials.

1. Introduction

The ability of living things to repair damaged tissue on their own is crucial to their existence. Any change to a tissue's structure, whether it be soft or rigid, is referred to as tissue damage. Living tissue is a complex, three-dimensional entity. Bones and teeth are examples of hard tissues, whereas ligaments, muscles, and tendons are examples of soft tissues. Soft tissues are any tissues that link and support various bodily organs and structures. Chemical, mechanical, or even pathogenic factors may cause tissue injury. Our bodies are designed to start a self-healing process called tissue regeneration to repair tissue damage. However, tissue/organ transplantation is the only option when the damage is so great that the body's self-healing system cannot keep up with the pace of cellular death or when the tissue is non-replicating. To put it another way, scaffolds are made to resemble the extracellular matrix and help the body heal itself when self-healing isn't enough. However, there are a lot of drawbacks to transplants, such as the scarcity of donors and the potential for transplant rejection.[1]

The extracellular matrix, the material that surrounds and serves as the physical environment for cells, is an essential part of tissues and organs. In tissue engineering and regenerative medicine, the extracellular matrix has so emerged as a model guide for the development and production of scaffolds and biomaterials. To support tissue/organ repair or reconstruction, this interdisciplinary discipline integrates practical medical sciences and engineering with fundamental sciences including cell biology, biomechanics, nanotechnology, polymer chemistry, materials science, and bioinformatics. However, creating a replacement tissue or organ or regenerating it is a very complicated process that frequently calls for a combination of multiple strategies, including the development of scaffolding with numerous purposes and the concurrent administration of cells, proliferation factors, immune-regulating agents, physiological signals, genes, growth variables and stimuli from outside.

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2. Discussion

Cells have the capability to distinguish between biomechanical signals from the matrix that surrounds them and from cells around them. They may then convert these cues into electrical and biochemical signals that control numerous cellular processes, including adherence, movement, growth, and transformation. Furthermore, cells on thin, soft coatings—that is, polymeric films placed on a hard material—are able to experience a firmer platform underneath and experience a complex firmness, which is the result of the stiffness of the hard substrate underneath as well as the upper soft material. The physiological, structural, and chemical attributes of scaffolds must be carefully adjusted to match the characteristics of the tissue that is affected. By choosing an appropriate technology for manufacturing, this can simply be achieved. For instance, the technique known as electrospinning works well when it comes to implantation in soft tissues or other tissues that need an elevated degree of elasticity. [2] Depending on the intended use and the desired location, a number of design choices about the necessary scaffold elements must be made.

However, just like electrospinning, extracellular matrix-like scaffolds may be created with a high level of complexity and accuracy using three-dimensional printing technologies, allowing for the inclusion of minute details down to the micron level. To get around the drawbacks of these traditional techniques, three-dimensional printing has emerged as a cutting-edge technology that could eventually result in the creation of matrix scaffolds that can more successfully encourage the regeneration of functional tissue. A promising technique for producing scaffolds with great accuracy and precision and producing finely detailed biomimetic three-dimensional structures is three-dimensional printing technology. Direct three-dimensional printing, fused deposition modelling, stereolithography, and selective laser sintering are among of the methods now being employed to accomplish the layer-by-layer process of three-dimensional printing scaffolds. Scaffolds with sizes ranging from millimeters to nanometers have been created using these methods. Additionally, it is noteworthy that during the past ten years, the terms additive manufacturing, three-dimensional printing, and solid freeform fabrication have become interchangeable. Creating adaptable scaffolds with intricate structures that can distribute cells uniformly and mimic the extracellular matrix are two benefits of employing three-dimensional printing.

The three main elements of developed tissues—growth-stimulating signals, scaffolds, and cells—are sometimes referred to as the tissue architecture trinity. Scaffolds are primarily built from biomaterials made of polymeric substances, and provide the skeletal framework required to facilitate cell attachment and the corresponding development of tissue. However, while choosing scaffolds for tissue engineering, researchers frequently run across a vast array of options. If an assembly method that is appropriate with the traits of the biological material is available, a wide variety of biomaterials can be used to develop permeable scaffolds for tissue engineering applications. Scaffolds were initially only utilized as supporting matrices. Other uses, however, had surfaced as tissue engineering progressed over time. Active compounds can be loaded onto scaffolds and delivered straight to the intended tissue or organ. For example, they might promote tissue regeneration and signal cell differentiation by transporting the right growth factors and signalling cues. [3] One approach to directly transport the medication to the intended damage location in appropriate dosages may be to include drug molecules within the scaffold. [4]

In order to facilitate good tissue healing, scaffolds must closely mimic the target tissue; otherwise, alterations in the niche tissue environment may occur, necessitating certain structural and physical considerations in scaffold design. [5] In order to promote host tissue integration after implantation, scaffolds should offer void volume for new tissue development, reorganization, and blood circulation. The post-implantation period ought to be meticulously taken into consideration while developing the scaffold. In addition to completely predestining the surrounding environment for the development of new tissue, implanted scaffolds should also guarantee that the signalling impulses are sent in the proper manner. The foundation of tissue engineering is, after all, signalling variables, such as growth factors, proteins, and medications.

Their primary purpose is to communicate a variety of processes, such as angiogenesis, receptor-mediated reactions, cellular infiltration, and differentiation, and even the start of scaffold breakdown and degradation. [5] Since any kind of incompatibility would hinder cells' capacity to regenerate new tissues, biocompatibility is crucial for both cell development and efficient tissue regeneration. [6] Scaffolds are necessary for the attachment, proliferation, and differentiation of endogenous or extraneously applied cells in both in vitro development and in vivo transplantation. Scaffolds may actively engage in interactions with the created tissues' biological constituents to promote and control their functions. The biomaterials might contain external factors like topography to affect cell shape and alignment or biological cues like cell-adhesive ligands to improve adhesion. Scaffolds provide the tissue defect form and mechanical stability. The scaffolding biomaterials' mechanical characteristics or their subsequent processing traits should correspond to those of the host tissue. The significance of a scaffold's mechanical characteristics for the planted cells has been emphasized by recent mechanobiology research. In addition to providing a suitable milieu to support the vascularization and innervation of new tissues, the

combination of gene delivery and multifunctional scaffolds enables precise manipulation of cell differentiation toward the intended phenotype. Immunomodulatory agent-loaded multifunctional scaffolds aim to address tissue healing issues related to scaffold/implant rejections.

To create scaffolds, naturally existing biomaterials can be extracted from their natural sources and treated. Extracellular matrix from allografts and xenografts are instances of these substances in their native arrangement. They can also be found in smaller building blocks, such as organic polymers like proteins, polysaccharides, lipids, and polynucleotides, and inorganic ceramics like calcium phosphates. In tissue engineering, the selection of biomaterials is very important. Both site- specific and generic qualities including biodegradability, biocompatibility, and non-toxicity should be met by biomaterials. For instance, it is obvious that a material that is readily processed is preferred over one that is rigid for delicate tissues like muscles or cartilage. Natural biomaterials often exhibit exceptional biocompatibility, allowing cells to adhere and proliferate with remarkable vitality. Natural materials may not be appropriate for some load-bearing applications due to their poor mechanical and physical stability. Because of this, scientists who work with natural biomaterials are motivated to create technologies that enhance and strengthen the materials' mechanical and structural stability. According to Sengupta et al. [7], scaffolds should break down naturally or through the action of enzymes that are often present at the target location, producing benign byproducts in the process. In order to guarantee appropriate tissue healing, the rate of degradation can either be slower or equivalent to the pace of new tissue development. [8] With developments in biomaterial science and newly proven manufacturing methods, scaffolding and tissue engineering have a bright future.

It has also been reported that biomaterials' surface adherence and biocompatibility can both be enhanced by nanocoating. [9] Leading the way in nanotechnology are nanoparticles, whose unique size-dependent characteristics have shown promise in resolving many of the current challenges in tissue engineering. The entire potential of nanoparticle applications in resolving tissue engineering issues has not yet been reached, despite significant advancements in their utilization over the past 20 years. Because of their excellent biocompatibility and proven surface modification techniques, nanoparticles are very useful in a wide range of biomedical applications. Nanoparticles have also been used to improve the electric connection between decellularized cells and proliferation rates across a variety of tissues. Research on the effectiveness of nanoparticles in inhibiting bacterial growth has also shown great promise. By being applied to biocomposite scaffolds, these nanoparticles have been able to control bacterial infection during reconstructive bone surgery.

Remotely controlled nanoparticles also encouraged the induction of cell mechano-transduction, which is in charge of numerous physiological processes in the body. In tissue engineering, nanoparticles have been employed for a number of purposes, including molecular detection, biosensing, gene delivery, DNA transfection, viral transduction, patterning of cells, and improving biological, electrical, and mechanical characteristics. The biological, mechanical, and electrical characteristics of scaffolds can be greatly improved by using the appropriate kind of nanoparticles in tissue engineering. Depending on the application, these nanoparticles can also perform a variety of other tasks. While silver nanoparticles have been demonstrated to have antibacterial activity in addition to enhancing the mechanical characteristics of the manufactured scaffolds, [10,11] gold nanoparticles have been discovered to improve the electrical properties of scaffolds in cardiac tissue engineering. [12–14] Furthermore, iron oxides, specifically Fe2O3 or Fe3O4, are magnetic nanoparticles. [15] These might target particular tissues with the use of an external magnetic field. They could also be applied to MRI and cell imaging. [16,17] Furthermore, the intended scaffold's electromechanical characteristics can be changed using carbon nanotubes. [18] Currently, a number of technologies are being researched before being released onto the market.

By carefully designing biocompatible materials and living cells layer by layer, bioprinting enables the fabrication of three-dimensional constructs that resemble tissue while maintaining tissue-level integrity. At this time, there isn't a single bioprinting technique or material that works for everyone. The techniques with the greatest significance have been laser-assisted printing, stereolithography, etc. The most often used materials have been both natural and manufactured, including collagen and hydrogels. Successful uses in tissue regeneration and drug-development models have been made possible by sophisticated bio-inks and three-dimensional bioprinting technology that preserve the viability and potency of cellular components, including stem cells. Additive manufacturing has made it possible to create scaffolds that are customized for each patient because of their versatility with regard to biomaterials and designs. However, it is necessary to comprehend how biomaterials and biophysical properties across various hierarchical structures impact biological cell behavior in order to construct a suitable scaffold with an appropriately optimized structure across diverse length scales. With this information, it would be possible to incorporate particular design elements into the scaffold to guide desired cell behaviors, maximizing regeneration for a variety of patient subgroups, including those with different biologically problematic limitations. Therefore, a real synthesis between patient-specific biological variables and physical scaffold design parameters is necessary to create

hierarchically constructed scaffolds for optimum tissue defect regeneration across various patient groups. Although, like many other indications, such personalized therapy concepts may be adequately addressed in today's cost-controlled healthcare environment by stratifying patients according to their gender, age, and ethnicity as well as any comorbidities. This would allow for the effective and efficient personalization of regenerative tissue therapy for each individual group.

3. Conclusion

A variety of characteristics, including mechanical and chemical characteristics, scaffold architecture, manufacturing processes, biocompatibility, biodegradability, or resistance, are necessary for the effective use of scaffolds in tissue engineering. [19] Numerous factors, including intracellular signals and intercellular and extracellular integrin–integrin and -ligand connections regulating cell–cell and cell–extracellular matrix interactions, influence the attachment and migration of cells along and/or across the membrane, which is a fundamental aspect of tissue formation or regeneration. [20] The commencement of diverse signals that further stimulate cell growth and differentiation depends on the focused cell adherence to the distinct scaffold surfaces. [21] Therefore, effective oversight of cell-cell and cell-scaffold coupling may help accomplish many of the goals of multifaceted tissue engineering.

In synthetic tissues, scaffolds are supposed to at least partially resemble the extracellular matrix seen in native tissues. Their roles should naturally resemble those of the target tissue's extracellular matrix. Four main scaffolding techniques have been developed over the past few decades: injecting cell-encapsulated self-assembled hydrogels; implanting cell-seeded pre-made porous scaffolds; implanting cell-seeded decellularized allograft or xenograft extracellular matrix; and implanting laminated cell sheets with secreted extracellular matrix. Every strategy has advantages and disadvantages as well as favored tissue engineering uses. These scaffolding techniques are useful recommendations for designing tissue engineering for complicated tissues and may be combined. The transport of biomolecules may be controlled spatiotemporally, extracellular matrix characteristics can be biomimicking, and scaffolds can be endowed with numerous functions thanks to micro as well as nanotechnologies. Research on the coupling of multifunctional materials with various therapeutic approaches—cell, gene, immunological, electric, magnetic, and light-based—indicates a strong trend. Cell administration combined with a multifunctional substance that naturally creates a milieu similar to the native extracellular matrix often leads to improved cell proliferation, differentiation, and tissue creation.

Tissue engineering and biomaterial sciences have emerged as new scientific disciplines in the past ten years, meeting the growing need for regenerative medicine. Combining a thorough understanding of cell biology with contemporary technologies to examine the biocompatibility of materials and their use in the repair of damaged organs and tissues is necessary for tissue engineering. Direct cell transplantation into injured tissues or blood vessels was the first step toward stem cell-based tissue regeneration. Tracking transplanted cells and maintaining them in a single location within a sick organ is challenging, though. New technologies have recently been developed extensively, such as the ability to cultivate stem cells on scaffolds and then transplant them into wounded tissue. Scaffolds with mechanical stability or biodegradability, the right size, surface roughness, and porosity are necessary for successful tissue regeneration because they create an ideal milieu for adequate cell-cell contact, migration, proliferation, and differentiation. The scaffold pore diameters, which are crucial for waste disposal and the passage of nutrients and oxygen, have a significant impact on the continued functionality of transplanted cells.

The issue of migration away from the implanted locations affects the majority of scaffolds. Crosslinkers are often added to the equation in order to solve this. However, their safety is a problem, thus it is necessary to provide information on the safest approach to stabilize the scaffolds at their intended location. The ex vivo method of tissue engineering is the way to go when dealing with non-replicating tissues, such nerve cells and heart tissue. This necessitates tissue development and ex vivo cell proliferation in an environment that is identical to its natural analogue. Even with the advancements in this area, repeatability remains problematic due to the difficulty of accurately simulating every aspect ex vivo. Although it is challenging to replicate nature, new scientific and technological discoveries indicate the possibility of creating multifunctional scaffolds that would support both systemic and local biological processes. In the creation of scaffolds in the future, careful consideration of the scaffold materials' shape, pore size and distribution, and capacity to release biomolecules at a certain pace will be crucial. Overall, the effective use of scaffolds in regenerative medicine requires a unique experimental optimization taking into account both therapeutic and regenerative goals.

However, this new technology also brings up a number of well-known and little-studied ethical issues. The technology is now in the early experimental stages of development, which presents well-known ethical challenges with relation to preclinical animal experiments. In addition, difficulties in conducting first-in-human trials and, in the case of pediatric disorders, involving children in such trials arise throughout the following clinical phase. [22–24]

Significant difficulties arise from the intricacy and unpredictability of the three-dimensional organ printing process, which includes problems with biomaterial degradation, tissue integration, biocompatibility, and ongoing tissue synthesis as material degradation occurs. An additional issue that is difficult to resolve is the possibility of permanent hazards, such as cancer and implant migration and dislodgement. [25–27]

An additional challenge is the inability to assess the organ's safety prior to implantation because it is produced specifically for the recipient and cannot be tested on other people. The problem is further complicated by the fact that organ implantation is extremely dangerous or impossible to reverse. In addition to the possible hazards associated with 3D bioprinting, the use of xenogeneic cells—which come from animals other than humans—may result in immunological and infectious problems. These foreign cells may cause immunological reactions upon introduction, which could lead to graft-versus-host disease or organ rejection. A major public health worry is the potential for cross-species disease transmission, which can bring novel pathogens into the human population. [28,29] Additionally, integrating stem cells with scaffolds is one of the main obstacles to putting three-dimensional bioprinting technology into practice. In tissue engineering, scaffolds are essential because they assist and direct the development of new tissues by acting as a three-dimensional scaffolding for the cells. Scaffold compositions including hydrogels, micro- and nanofibers, and micro- and nanospheres are employed. There are pros and cons associated with each kind of scaffold formulation. For example, microfibers may provide a more favourable time course for medication delivery, but hydrogels promote cell survival and proliferation. Additionally, by combining these various scaffolds, new hybrid materials can be produced, frequently utilizing the special advantages of each formulation to maximize drug delivery and cell survival. To guarantee successful bioprinting and tissue growth, it is difficult to strike the correct balance and integrate these many materials. [30]

The source of the biological components utilized in three-dimensional bioprinting is another major ethical issue. Adult stem cells and human embryonic stem cells are now the sources of cells for bioprinting, as was mentioned in the introduction. Because it entails the death of human embryos, the use of embryonic stem cells is especially controversial and raises moral and ethical concerns about the worth and sanctity of human life. On the other hand, since adult stem cells and induced pluripotent stem cells do not require the death of embryos, their usage may be regarded as more morally acceptable. [24–29,31–34] Because life begins at conception, some people believe that an embryo has the same moral rights as an adult or a child. They contend that an embryo is a person with rights and interests that should be protected. They believe it is murderous to remove cells from a blastocyst in order to produce an embryonic stem cell line. Unquestionably, in order to guide judgments in this complex and constantly evolving subject, it is imperative that science, society, and ethics have an open and continuous dialogue.

Furthermore, cooperation between numerous parties with disparate interests is necessary for the development of these implants. This gives rise to further and more focused ethical and practical issues with scaffold commercialization, like conflicts of interest and concerns about accessibility of this potentially costly technology. [35,36] Since this technology is still in its infancy, it is unclear how these scaffolds are viewed and comprehended, which presents fresh ethical dilemmas regarding their ontological standing and their impact on physiological experiences and human identity. For the testing and eventual clinical use of such implants, this has additional ethical implications. In order to give the best care possible for each patient, it is also necessary to take into account less evident and less studied ethical issues, such as the incorporation of gender variations in implant design. To support the development of customized 3D printed scaffolds in a responsible, secure, and morally sound manner, it is crucial to map all these factors early in the process rather than at the end. [37]

To promote responsible innovation in tissue engineering, it is crucial to make sure that ethical issues are not an afterthought but rather a fundamental component of the research process. The methodical integration and application of ethical ideas in the field might be aided by three crucial elements. First and foremost, it is imperative that ethics education and training be integrated into tissue engineering research at all levels. Universities, companies, and research institutes should create and provide thorough ethics workshops and courses that are especially suited to tissue engineering. A broad range of ethical subjects ought to be covered in these courses. Second, it is crucial to define and update ethical criteria for tissue engineering research in a collaborative manner. These ethical principles should be easily available, unambiguous, and flexible enough to accommodate changing practices and technologies. Ideally, they should be incorporated as an essential component of the current (regulatory) guidelines in tissue engineering. Third, a comprehensive approach to ethical issues can be fostered by encouraging interdisciplinary collaboration amongst all stakeholders, including tissue engineers, ethicists, healthcare practitioners, end users (patients), and legislators. Early in the study process, these partnerships allow researchers to recognize ethical issues and collaborate to find solutions.

Establishing strong, adaptable, and inclusive ethical and regulatory frameworks that keep up with the rapidly changing technological landscape is crucial as we venture into the unexplored realm of three-dimensional bioprinting. These frameworks ought to handle the numerous ethical, legal, and regulatory issues that

three-dimensional bioprinting raises while encouraging its responsible development and application. In order to educate these essential foundations and create an atmosphere where technological advancements enhance rather than contradict our moral and legal commitments, this scoping review emphasizes the necessity of continual, multidisciplinary research and discussion.

4. Conflict of interest

None.

5. Source of funding

None.

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