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Virus Decorated Nanobiomaterials as Scaffolds for Tissue Engineering

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Abstract

One of the applications of tissue engineering is to develop artificial scaffolds. These scaffolds can mimic extracellular matrix and support cells for the repair of damaged tissue and organs. Virus particles can be re-engineering by genetic and chemical modification. Scaffolds can support cell growth and regulate cellular functions such as adhesion, spreading and proliferation. Scaffolds can be two dimensional or three dimensional which are resulting from self-assembly of the re-engineered. In this review, we review the role of virus based scaffolds in vivo and their applications in tissue engineering.

Keywords: Scaffolds, Tissue engineering, Virus-based nanoparticles, Nanomaterials

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1. Introduction

The loss or failure of an organ or tissue is one of the most common, devastating and costly problems in health care. The purpose of tissue engineering is to solve these problems. Engineering stems from the demands by surgeons in regenerating functionally active tissue to replace lost tissue. Tissue loss may be due to injury, trauma, microbial invasion or congenital problems. [1] Current methods for organ and tissue replacement mainly utilize autografts, allografts, or metallic devices. These methods face serious limitations including donor site morbidity, Shortage in supply, poor. Integration and potential immunologic reactions. These limitations emphasize the importance of the development of tissue engineering.[2] In tissue engineering, growth factors are introduced into the scaffolds to guide cells behavior in the desired direction. [3] The inability of engineered materials to mimic the natural properties of tissues is one of the existing obstacles that can be overcome with the help of nanotechnology. The advantage of nanoparticles in tissue engineering stems from their small size and associated large surface to volume ratio, which is comparable to peptides and small proteins. The size of nanoparticles is not limited by a predetermined size, as they can be customized in sizes and Surface properties to suit any purpose.[4] The nanoparticles also mimic the natural nanometer scale of the extracellular matrix components of the tissues themselves.[5-7] Another advantage of virus-based nanoparticles is that they can be produced in gram quantities with high uniformity in the laboratory.[8] virus-based nanoparticles provides addressable Platforms for nanoscale manipulation, since site-selective function can be performed on virus-based nanoparticles, based on the knowledge of their structures.[9, 10] Of the viruses, plant viruses have the certain advantages. Plant viruses are not pathogenic to animals, and they also their empty non-infectious capsids can be easily and rapidly produced to high yields using plants (41 g/kg fresh plant weight) in a manner which is Conductive to up scaling. [11-13]

Plants viruses include: Brome mosaic virus, Potato virus X, Tobacco mosaic virus, Cowpea chlorotic mottle virus, Cowpea mosaic virus, etc.

In the past ten years, researchers have explored a variety of biomimetic nanocomposites by incorporating bioactive molecules, such as growth one factors, cytokines, genes, antibiotics and anti-inflammatory drug within the scaffold to increase tissue regeneration potential. [12, 14, 15]

2. The importance of scaffolds

Most tissue engineering approaches involve the isolating and expanding cells in vitro. Tissue engineering requires a large number of cells to function properly, while fully differentiated cells have limited.

Three common strategies employed in tissue regeneration: infusion of isolated cells, treatment with tissue inducing substance, and implantation of a cell scaffold composite. Of these three strategies, the use of cell scaffold composites often lead to more successful results. These scaffolds are often critical, both in vivo as well as in vitro, to recapitulating the normal tissue development process and allowing cells to formulate their own microenvironment.

In contrast to using cells alone, a scaffold can promote cell and tissue development by providing a 3D environment in which cells can proliferate, attach and deposit extracellular matrix. The scaffold also provides structural stability for developing tissue and allows incorporation of biological or mechanical signals to enhance tissue formation.

Scaffolds at the microscopic level have a porous structure for diffusion of nutrients and waste products (figure 1). [16-18]

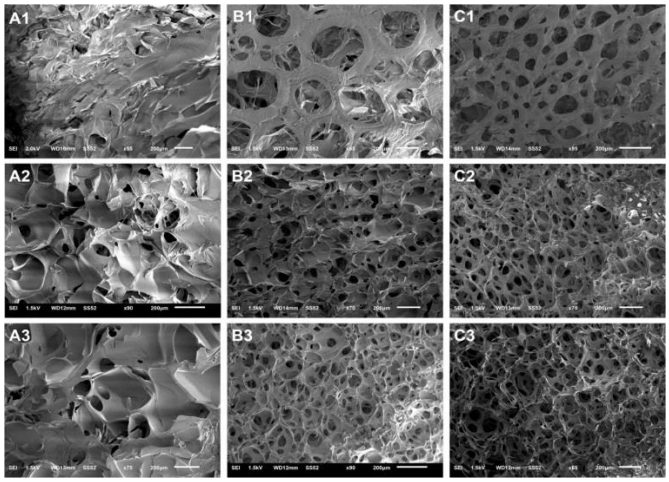

Figure 1 : Pictures of different pore sizes in scaffolds made of Gelatin 5% w/v foamed at 0 (A1), 500 (B1) or 1500 (C1) rpm, 10% w/v foamed at 0 (A2), 500 (B2) or 1500 (C2) rpm, 15% w/v foamed at 0 (A3), 500 (B3) or 1500 (C3) rpm. Adopted [19]

The optimal pore size depends on the specific cell type. These pores must be large enough to allow cell migration and extracellular matrix formation. If the pores are smaller than a certain limit, the pore occlusion occurs. The scaffold surface architecture and chemistry should facilitate cell migration through the scaffold provide developmental signals to the cells, and promote cell recruitment from the surrounding tissue. Additionally, the most cases the scaffold should be constructed from a degradable nontoxic material. [2]

Biodegradability is a feature of an ideal material for tissue engineering as it is essential to avoid an invasive implant removal procedure after the new functional tissue has been developed in the patient. Moreover, the degradation of the scaffold must closely follow the extracellular matrix synthesis and macroscopic tissue development. Thus, the rate of degradation of biomaterial of biomaterials scaffolds is desired to correspond with the development of a type of tissue that replaced.[8] Organic and inorganic materials are amalgamation with scaffolds to increase morphology and mechanical properties, thus supporting better cell attachment and proliferation.[20]

3. The role of virus-based nanoparticles in tissue engineering

Viruses have been exploited the fabrication of nanostructural materials[21] and have a great advantages including high architectural uniformity, monodispersity and a variety of distinctive shapes (spheres, tubes and icosahedrons) and sizes (from 10 nm to 1 μm).[22] The multivalency of viruses would allow multiple display of cell signaling motifs to enhance the binding affinity with cell surface receptors. Viruses without external envelopes are ideal for nanomaterials fabrication because the functional groups on the capsid proteins can come into direct contact with organic and inorganic materials. Among viruses, plant viruses that are harmless to humans, are commonly used for the fabrication of virus mediate nanomaterials.[23, 24] Animal viruses are less commonly used, since the safety concerns. Another group of viruses used is bacteriophages, which are used in molecular biology studies because they are amenable to genetic modification. [21]

Tobacco mosaic virus, a plant virus, was the first virion to be purified in 1935. [25, 26] Tobacco mosaic virus has been a model for understanding the properties of viruses for over a hundred years. As a result, the structural and physicochemical properties of tobacco mosaic virus are well understood and tobacco mosaic virus has become an ideal biotemplate model for synthesis of nanomaterials. Genetic engineering allows enables the redesign of the physicochemical properties of the tobacco mosaic virus coat protein. Tobacco mosaic virus is biologically stable at pH 2.5-9.0 and at temperatures up to 60°C. This makes tobacco mosaic virus a promising scaffold for nanofabrication. [4, 21, 27]

Virus templates are used for the fabrication of hybrid nanomaterials because of the similarity of viruses to protein assemblies. In addition to the tobacco mosaic virus mentioned, wild-type cowpea chlorotic mottle virus has also been used as a virus template. Icosahedral protein cages of cowpea chlorotic mottle virus were first used as scaffolds to mineralize polyoxometalate species and to encapsulate anionic polymers. [21, 28, 29]

Although early research used inorganic substances with viruses, organic substances are more successful because the conjugation of organic substances with viruses provides an effective means of diversifying active interfacial functionalities. In comparison to inorganic substances, organic molecules are flexible and more reactive to biomolecular scaffolds. The bioconjugation of organic molecules with viruses require active moieties on capsid proteins that perform chemical reactions under ambient physiochemical conditions. These active moieties should be located in positions that enable the easy access of organic molecules without impediment. In addition, the conjugated organic molecules should be located in an area of the virus that does not destroy the structure and assembly of proteins while maintaining original property of virus.[21, 30]

Several nanoparticle platforms are currently being developed for applications in medicine, including both synthetic materials and naturally-occurring bionanomaterials such as virus-based nanoparticles and their genome-free counterparts virus-like particles. virus-based nanoparticles and virus-like particles are assembled from protein subunits whose structure and physicochemical properties can be modified by genetic engineering.[31-33] This is a quite advantage whereas chemical modifications are not 100% efficient.[32, 34] the basic virus-based nanoparticles structure can be 'programmed' in a number of ways so that the internal cavity can be filled with drug molecules, imaging reagents, quantum dots and other nanoparticles, whereas the external surface can be decorated with targeting ligands to allow cell-specific delivery.[34-37] Initial research focused on the deposition of unmodified virus-based nanoparticles such as cowpea mosaic virus onto glass surfaces by nonspecific adsorption, followed by an assessment of their ability to promote cellular growth compared to nontreated control slides.[38-40]These experiments showed that cowpea mosaic virus biofilms significantly enhanced cellular adhesion and proliferation, and experiments were therefore designed to see if further enhancement could be achieved by coupling relevant ligands to virus-based nanoparticles using a two-step conjugation process: diazonium coupling of an alkyne to tobacco mosaic virus followed by CuAAC to introduce the RGD peptide ligand.[41-43] When deposited onto glass slides, tobacco mosaic virus displaying RGD peptides was able to promote the adherence of NIH-3T3 cells more effectively than wild-type tobacco mosaic virus or tobacco mosaic virus derivatized with a long-chain PEG polymer. Similar work was carried out in which the plant viruses were replaced by RGD-modified M13 particles deposited onto glass surfaces using a "slow dragging" method that caused them to align along the long axis of the virus-based nanoparticles.[44, 45] When NIH-3T3 and CHO cells were deposited onto the film, they grew along the axis of virus-based nanoparticles orientation, leaving the researchers optimistic that this approach could be generalized for multiple cell-types and/or ligand presentation.[46] The above techniques have been developed to encourage the differentiation of stem cells from progenitor to adult cells, specifically in the case of osteogenesis. Glass slides coated with either the rod-shaped tobacco mosaic virus or the icosahedral turnip yellow mosaic Virus encouraged bone marrow stromal cells to undergo osteogenic differentiation at significantly enhanced rates compared to cells grown under standard conditions. [47, 48] The addressable tobacco mosaic virus platform was then used to introduce chemical cues for differentiation, to complement the natural biogenic properties of virus-based nanoparticles.[49, 50] A two-step "diazo-click" reaction (diazonium coupling of alkynes followed by CuAAC) allowed tobacco mosaic virus particles to be decorated densely with phosphate groups. The tobacco mosaic virus -Phos biofilm attracted calcium ions onto the tissue culture surface and increased calcium uptake by BMSCs, promoting differentiation into osteoblasts as shown by the upregulation of several relevant markers including osteocalcin, osteopontin and runx2. Titanium substrates were prepared with a tobacco mosaic virus -Phos coating and assayed in a similar manner. As expected, these surfaces also encouraged osteogenic differentiation. The results of this study were remarkable considering the chemical simplicity of the film relative to the biological outcome, suggesting that simple cues displayed on a biocompatible surface can be used to reprogram tissues.[51] As viruses have shown great potentials in tissue engineering applications, the biosafety must be taken into consideration for future in vivo applications. Many works have been done to investigate the fate of these viral nanoparticles in vivo and evaluate their toxicity, including the blood clearance, bio-distribution, biocompatibility and pathology.[52, 53]

Overall, the recent rise of virus-based nanoparticles -based tissue engineering articles, emphasizes the immense promise offered by virus-based nanoparticles biogenic materials.[54] It can be hoped that biocompatible virus-based nanoparticles will play an important role in the development of novel materials for tissue engineering. [51, 55]

4. Bone and Neural tissue engineering

One of the most important subjects in tissue engineering is inducing bone regeneration. [56] Studies is showed that we can cultured bone marrow stromal [57] cells in ex vivo situation and they could differentiate into osteoblast, chondrocytes, adipocytes, tenocytes, and neural cells. [58] So for bone tissue engineering, building active scaffold, for bone marrow stromal cells to differentiate into other cells is an appropriate method. The interactions between bone marrow stromal cells and underlying substrates is so important to regulate the osteogenic or chondrogenic processes,[50, 59, 60] therefor some studies have been done to use engineered viruses as platforms.[53, 61] Another type of tissue engineering used nowadays is neural tissue engineering, which is one of the most promising treatments for spinal cord injury. [62] The scaffolds used cause neural progenitor cells to adhesion and direct the differentiation of neural progenitor cells into neurons. This shows the importance of topographic and biological signals of biomaterials for in vitro cell culture and in vivo neural tissue engineering applications (figure 2). [61, 63]

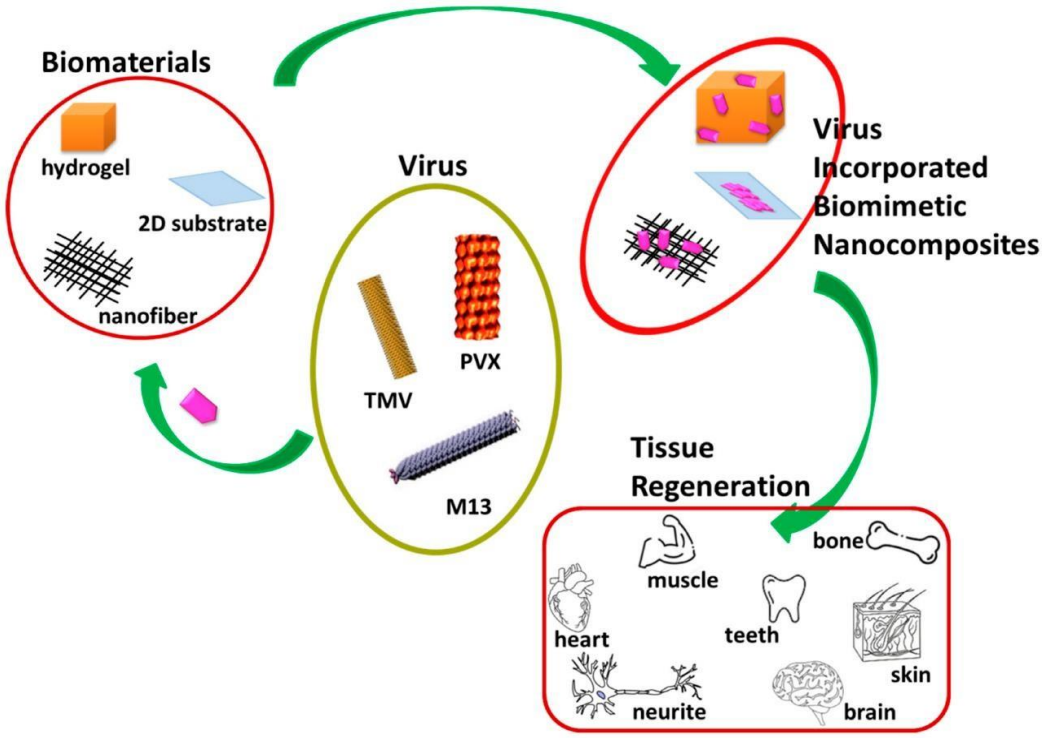

Figure2: This image shows the path of tissue engineering with the help of viruses. Here are Potato Virus X (PVX), Tobacco Mosaic Virus (TMV), bacteriophage M13 viruses as an example. Adopted [12].

5. Conclusion

The great potential of tissue engineering has led the field to grow rapidly over the past two decades, but most regenerative therapies are still in the developmental phase. Viruses are biological scaffolds that are applicable to a variety of nanotechnologies. [64] Mass production of viruses with uniform size, complex structure and diverse chemical moieties makes them a promising template for nanomaterials fabrication. [8] Viral scaffolds can bind well to organic and inorganic substances, making them highly desirable, highly functional biological scaffolds. For tissue engineering the chemical, morphological, and mechanical properties of scaffolds must be tuned to optimize interactions with the cells and the surrounding tissue, whereas the biodegradation rate must be controlled to preserve the scaffold's integrity until the maturity of the growing tissue. When selecting and developing new materials for tissue engineering, it is imperative to simultaneously consider the complex biochemistry, morphology, mechanical behavior, and biodegradation characteristics of the scaffold. This review illustrated the path and challenges facing tissue engineering to viral scaffolding and sought to emphasize the importance of this issue.

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