GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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Overview of implantable and injectable biomaterials in immunotherapy

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GSC Biological and Pharmaceutical Sciences, 2021, 16(01), 195–201

Publication history: Received on 19 June 2021; revised on 25 July 2021; accepted on 27 July 2021

Article DOI: https://doi.org/10.30574/gscbps.2021.16.1.0208

Abstract

Immunotherapy has shown promising applications in cancer treatment as it boosts the systemic immune response. Existing immunotherapy strategies have certain drawbacks which can be addressed by engineered biomaterials. In this review, we focused on advanced immunotherapy methods involving implantable and injectable biomaterials for the treatment of cancer. Engineered biomaterials as carriers for immunomodulatory agents aid in the local drug delivery, thus reducing the frequency of off-target side effects. Also, biomaterial-based cancer vaccines have the potential to target specific tissues by finely altering the physical properties of the drug to achieve desired drug release kinetics.

Keywords: Immunotherapy; Implantable biomaterial; Injectable biomaterial; Hydrogels; Colony stimulating factors (CSFs)

1. Introduction

The earliest definition of biomaterials was developed in 1972, during the Consensus Conference of the European Society for Biomaterials (ESB), during which biomaterial was defined as *'a nonviable material used in a medical device, intended to interact with biological systems*; As per the current definition, it is a *'material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body* [1,4]. This change in definition is suggestive of how the field of biomaterials has changed. Biomaterials have moved from merely interacting with the body to prompting biological processes toward the goal of tissue regeneration [1,4]

Tissue engineering is an interdisciplinary field that includes material science, genetics, clinical medicine, mechanical engineering [2]. It is the application of engineering and life sciences towards repair, restore and improve the function of tissue or a whole organ.

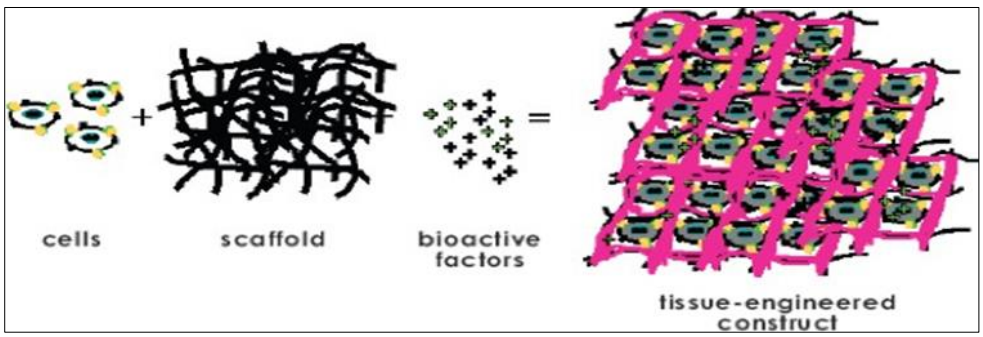

Figure 1 Main components of the tissue-engineered construct [1]

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This utilizes Scaffold for structural support and environment for cell proliferation, adhesion, and Extracellular matrix deposition until new tissue is completely restored [3]. Furthermore, the scaffolds are combined with growth factors, cells, and other signaling molecules that represent the key elements of tissue engineering (fig 1) [4]. After integration into host tissue, scaffold material should not elicit an immune response to avoid inflammatory reactions that might reduce the healing or result in rejection [5].

2. Biomaterials in immunotherapy

Recently, synthetic and natural biomaterials have become important elements in tissue engineering and regenerative medicine [4]. Several types of biomaterials have been currently used with key properties such as biocompatibility, biodegradability, bioactivity, based on applications these materials must be carefully designed and synthesized to fulfil their role. The use of biomaterials can elicit adverse reactions by the immune system, recognizing it as foreign origin, which interferes in the drug delivery system. Thus, it is noteworthy in understanding the interactions involved between biomaterials and the immune system [6].

In the case of implants, the foreign body response is a two-step process consisting of an inflammatory reaction followed by wound-healing [7] which triggers the accumulation of a thick layer of collagen on the implant. This deteriorates the efficacy of implanted material [7, 8]

The potential applications of biomaterials involving synthetic nanoparticles and microparticles, lipid carriers, injectable scaffolds, and hydrogels are directed to the field of immunotherapy. These materials can be designed not only to release immunomodulatory factors but also to navigate the host immune response [9-11].

The immune system plays a vital role in the prevention of tumor development and cancer [13-15]. Cancer immunotherapy invokes the activity of the intrinsic immune system to fight cancer cells [16-20]. Immunotherapy can be defined as the treatment that uses certain substances to suppress or stimulate the immune system to fight against cancer, infection, or other diseases. This recent development in the treatment of cancer has led to the eradication of systemic tumor, in contrast to traditional chemotherapies which uses cytotoxic drugs to act against cancer cells [12]. As yet, there are three main types of cancer immunotherapy which include, cancer vaccines [21-23], immune checkpoint blockades [24-26], chimeric antigen receptor-modified T cells [27]. These immunotherapeutics have shown excellent success in treating some tumor types but still, some challenges persist.

Engineered biomaterials that are injectable, implantable, and transdermal devices (fig 2) have paved the way in the development of localized delivery systems for immune therapeutics [28-35]. Advanced biomaterials are designed and developed to optimize the pharmacokinetics of the drug, controlled drug release, and increased drug retention within the target site while reducing immunotoxicity.

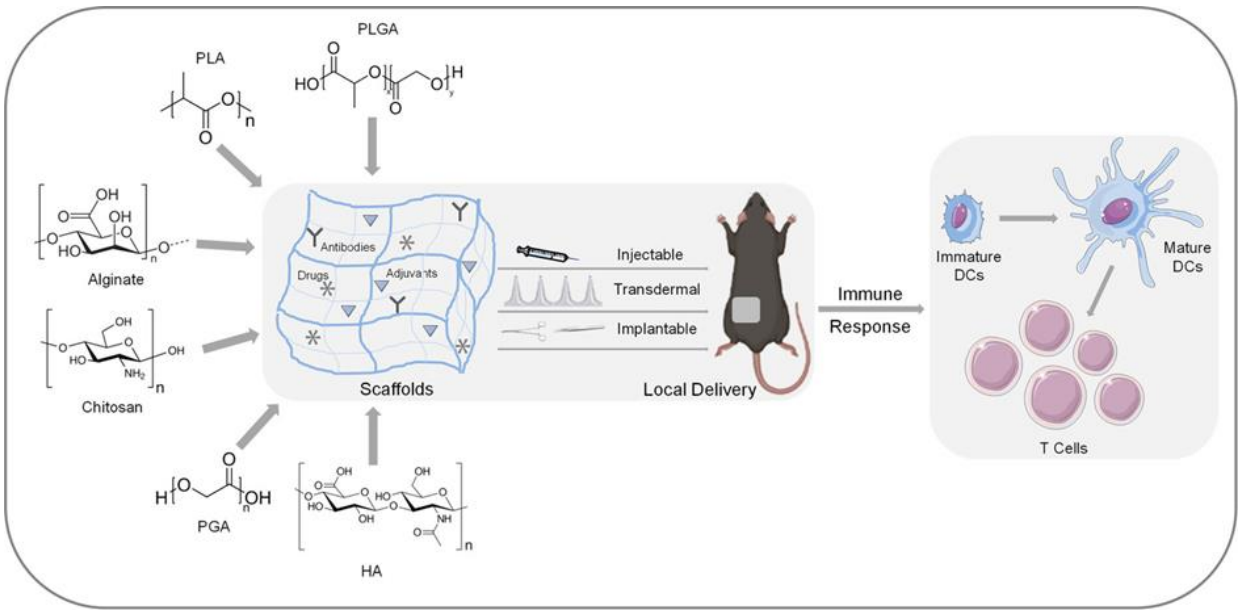

Figure 2 Representation of engineered biomaterials in cancer immunotherapeutic [36].

3. Implantable biomaterials

Implantable biomaterials are implanted subcutaneously or at the site of excised tissue via surgery. Before implantation, biomaterials are preloaded with various chemical substances, biologic factors, or bioactive agents. These bioactive agents are released in a controlled fashion from a porous scaffold matrix, and immune cells are recruited at the site [37, 38]. Engineered biomaterials such as polyglycolide (PGA), chitosan, hyaluronic acid (HA), polylactide (PLA), alginate, and poly (lactic-co-glycolic acid) (PLGA), are utilized to create porous scaffolds that encapsulate therapeutic substances in injectable, implantable, or transdermal delivery systems [fig 2]. Further, immune responses such as the proliferation of T-cells and maturation of dendritic cells are activated by localized drug delivery [36].

Antigen-presenting cells (APCs) such as dendritic cells play a major role in initiating humoral and cellular immune responses by presenting tumor-associated antigens in different ways. This mechanism has been studied in mouse cancer models, wherein dendritic cells capture antigens from dead or live tumor cells and present the antigens to T cells in tumor-draining lymph nodes. Further, this resulted in the production of tumor-specific cytotoxic T lymphocytes (CTLs) [39].

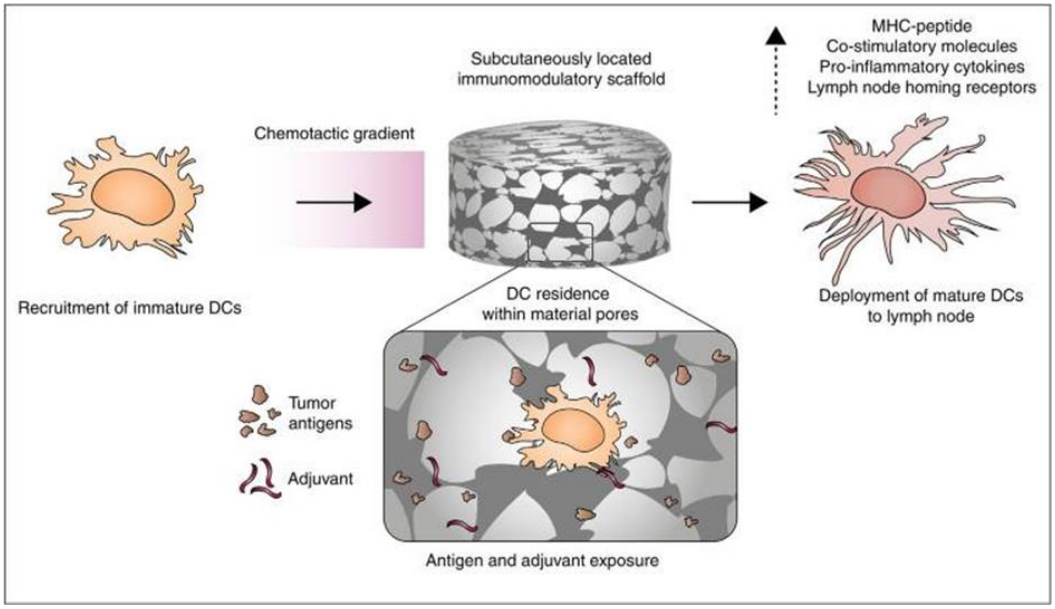

Figure 3 Implantable porous scaffold designed to release chemoattractants in order to recruit immature dendritic cells [39]

Several types of biodegradable polymers such as PLG are used in implantable drug-delivery scaffolds. PLG is extensively used in cancer immunotherapy due to its ease of surface modification, customizable biodegradation rate, high biocompatibility, and FDA approval for clinical use. A novel method was devised to prepare uniform PLG scaffolds of molecular mass 120kD in 85:15 ratio of copolymer D,L-lactide, and glycolide using a gas-foaming process [40]. PLG scaffolds are used to encapsulate hematopoietic cytokine, granulocyte-macrophage colony-stimulating factor (GM-CSF) that induces expansion of DCs, macrophages, and neutrophils. It also inhibits the proliferation of cancer cells via immune-independent effects and regulates T-cell proliferation and activation. GM-CSF attracts DCs that engulf apoptotic tumor cells. Release of GM-CSF from the scaffold induces DC maturation. The mature DCs then migrate to draining lymph nodes and present tumor antigen to T cells. This results in T-cell activation and expansion, enhancing the antitumor immune response (fig 3) [39].

On contrary to traditional cancer vaccines, an implantable GM-CSF delivery system can release GM-CSF continuously for 2 weeks, resulting in a longer immune response [41]. In a melanoma mouse model, the survival rate increased significantly after implanting PLG scaffold encapsulated with tumor-associated antigens, and GM-CSF.

Implantable delivery systems with modified biomaterial scaffolds have several advantages due to their ability to control the release of immune cell recruitment factors, continuous release of bioactive agents for a sustained period, and various other functions. One of the drawbacks of the implantable delivery system is the requirement of surgery, this can become a potential source of infection [36].

4. Injectable biomaterial

Implantable biomaterials have certain limitations that have led to the development of injectable immunotherapeutic biomaterials. Injectable biomaterials include cryogels, hydrogels, and other *in-situ* systems derived from synthetic or natural sources [12]. These materials enable controlled and localized release of the drug (fig 4). Injectable material can be modified for easy move and flow across the membrane, thus conforming to any accessible site [42]. An injectable therapeutic system avoids any tissue damage and complications associated with an inflammatory wound response. It is a less invasive procedure compared to surgical implantation.

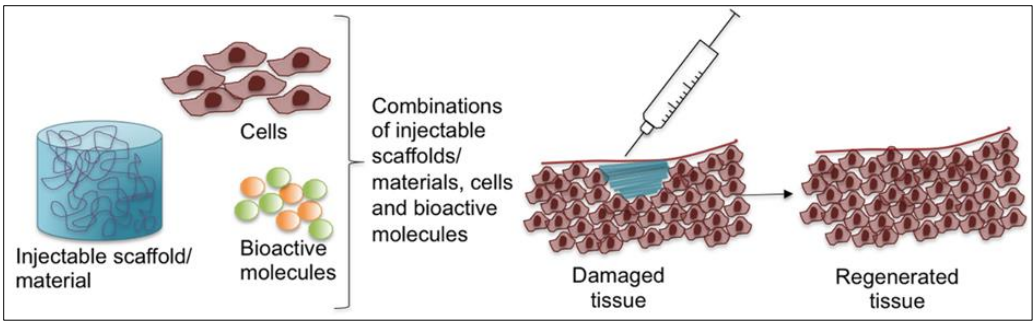

Figure 4 Injectable biomaterial in tissue regeneration [46]

In the recent research carried out by Bencherif et al., an alginate-based cryogel biomaterial was studied as an injectable cancer vaccine using CpG as a danger signal, GM-CSF for cell recruitment, and irradiated melanoma cells as antigen source. RGD peptides were incorporated into the cryogel for better adhesion of irradiated melanoma cells. Thus, resulted in sustained release of the immunotherapeutic factors [43,44].

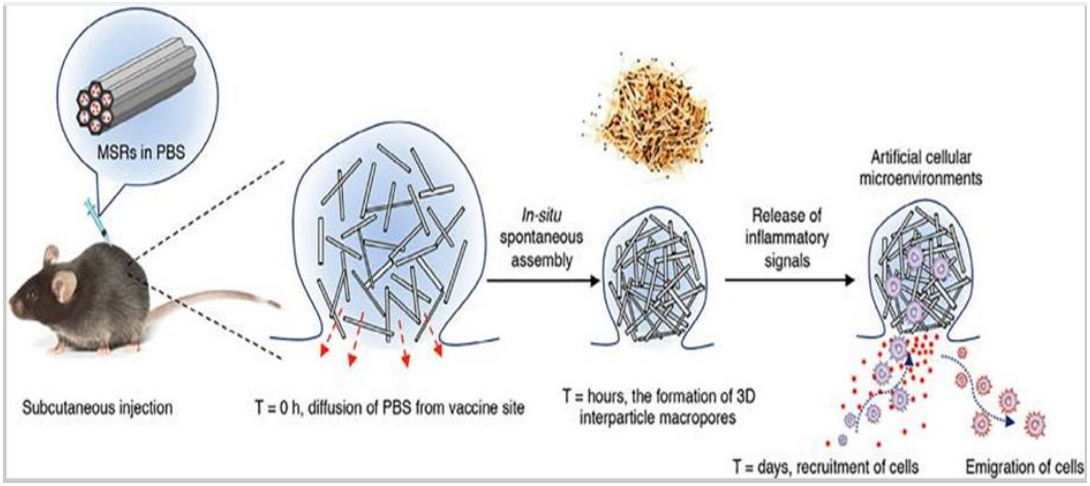

Figure 5 illustration of MSR assembly and cell recruitment in vivo [48]

Injectable hydrogels are currently applied for designing cancer vaccines. An injectable smart hydrogel was designed similar to extracellular matrix that self assembles into the microporous network, and by using simple hypodermic needles it can be injected subcutaneously. Scaffold for encapsulating GM-CSF and ovalbumin has been constructed with a temperature-responsive copolymer of PCLA and PEG combined with HA. A single injection of this loaded hydrogel into B16/OVA mice enhanced the recruitment of DCs and other immune cells to the tumor site and led to substantial inhibition of tumor growth [45].

Injectable hydrogels have shown potential tumor growth inhibition and prevention of recurrence in combination therapy in vivo. Fibrin hydrogel possesses excellent biodegradability and biocompatibility. It was loaded with chemotherapeutics cyclophosphamide (CTX; a small molecule drug) and anti-PD-L1 (an immune checkpoint-blocking monoclonal antibody). The drug release kinetics of CTX and anti-PD-L1 vary widely due to their large size difference. CTX being the smaller molecule is released first from the fibrin gel, thus creating an immunogenic tumor microenvironment. This generates a synergistic antitumor effect due to staggered delivery of the immune checking-

blocking antibody and small molecule from the fibrin gel reservoir. Further, it was evaluated in mouse models of ID8 ovarian cancer and TNBC 4T1 breast cancer, resulting in increased inhibition rate of tumor recurrence after surgery [47].

Kim et al. in 2014 developed a strategy for injectable cancer vaccine scaffold based on mesoporous silica rods (MSRs) [48]. It is a well-designed compromise between implantable scaffolds and injectable biomaterial that self-assembles into a separate pocket-like depot when injected subcutaneously (fig 5). When the scaffold is pre-loaded with CpG, GM-CSF, and other molecules, it creates a depot of immunotherapeutic agents that is capable to recruit and influence local immune cells [48].

A recent development in injectable biomaterials involved the application of hydrogel spray onto the surface of the tumor site after the surgery, to inhibit the tumor regrowth by increasing the pH of the tumor environment. This spray consists of FDA-approved fibrin gel to encapsulate $CaCO_3$ nanoparticles loaded with anti-CD47 antibody. CaCO3 nanoparticles serve as a reservoir for releasing immunomodulatory antibody as well as a proton scavenger that reduces the pH of tumor environment. When it is sprayed onto the tumor site post-surgery, the CaCO3 nanoparticles dissolve and release the encapsulated anti-CD47 antibodies which activates the macrophages to engulf cancer cells and inhibit tumor recurrence at the site [36, 49].

5. Conclusion

Current developments in immunotherapy and biomaterials have paved the way for a promising approach towards overcoming clinical limitations in the field of cancer immunotherapy. These advancements were depicted in this review showcasing the exciting potential of engineered biomaterials in drug delivery systems, whether it is in the form of implantable or injectable. Over the past few decades, Immunotherapy strategies have shown promising clinical results. Yet they possess certain limitations such as systemic side effects, poor delivery kinetics, and narrow patient response profiles. Engineered biomaterials overcome these problems, allowing tunable drug release kinetics up to several days or months depending on the design of biomaterials, improved efficacy, and reduced side effects.

Compliance with ethical standards

Acknowledgments

The authors would like to thank the staff of RV College of Engineering for their technical support towards this review paper.

Disclosure of conflict of interest

There are no conflicts of interest to disclose.

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