Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Review Article

Exploring Biomaterials for Cancer Immunotherapy: An Updated Review

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ARTICLE DETAILS

Article history:
Received on 6 June 2019
Modified on 1 July 2019
Accepted on 7 July 2019

Keywords:
Biomaterials,
Cancerimmunotherapy,
Bioscaffolds,
3D Cancer Model.

ABSTRACT

Cancer immunotherapy is an ever growing approach in cancer treatment. Its' capability to reactivate immunity against cancer, reducing cancer immune evasion, long term metastasis and recurrence further exemplify the potential to revolutionize cancer treatment. Currently available cancer immunotherapies especially cell-based immunotherapy suffer from several setbacks including the loss of HLA-1 molecules, immunosuppresive microenvironment and release of immunosuppresive molecules, all which may compromise their therapeutic effects. Recent advancement in biomaterials might present a solution to these problems. In a cancer immunotherapeutical perspective, many studies have reported the use of biomaterials in scaffolds, delivery systems, immunomodulatory adjuvants and immune cell engineering. Generally, the use of biomaterials increases specificity and decreases side effects. In this article, we provide an overview of the current perspectives of biomaterials application in cancer immunotherapy, its advantages and setbacks, and the future consideration for the use among other modalities in cancer immunotherapy.

INTRODUCTION

Nascent cells develop constantly but are regularly recognized and eliminated by the innate immune system. However, when nascent cells escape elimination, they start to grow under immune pressure acquiring the required traits to survive and overcome the immune pressure through various mechanisms [1]. The growing tumor will then show the ten hallmarks of cancer, in which each of the hallmarks presents an opportunity as a treatment modality for cancer [2].

One of the treatment perspectives gaining popularity is cancer immunotherapy with its capability of reactivating the body's immunity against cancer.Moreover, cancer immunotherapy is also capable of reducing cancer immune evasion, long-term metastasis and recurrence [3]. Some currently available immunotherapy includes dendritic cell-based immunotherapies (Sipuleucel-T), immunostimulatory cytokines (IL-2), immunomodulatory monoclonal antibodies (CTLA4-dependent checkpoint blockers and PD-1-dependent checkpoint blockers) and tumor-targeting monoclonal antibodies (VEGFA neutralizers) [4]. However, many immunotherapies, especially cell-based immunotherapy, may present issues such as the loss of HLA-I molecules and an immunosuppressive microenvironment of the tumor microenvironment [5]. Furthermore, several immunosuppressive molecules released by tumors such as arginase, indoleamine 2,3-dioxygenase (IDO), and prostaglandin E2 reduces the effectivity of T cells [6].

Biomaterials are micro- or nano- formulations, implants or scaffolds that deliver beneficial cargoes for the enhancement of immunotherapy and reduction of side effects [3].They have greatly increased in sophistication due tothe development of novel synthetic methods and progress in the understanding of biological processes, resulting in their transition from being a merely structural support to a potent tool capable of interaction to cells and tissues through known molecular pathways [7]. To date,

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there are six formulations of biomaterial, namely lipid-based, polymeric, inorganic, virus-like, scaffold and microneedle, each with their own merits and demerits which will be discussed below [3].

In this review, we summarize the current evidence for the role of biomaterials in the field of cancer immunotherapy: as an intricate and accurate 3D cancer models for in vitro studies and immune-engineered structure for cancer therapy.

Biomaterials as 3D Cancer Models

Generally, human cancers have been investigated in conventional way using 2D monolayer models [7]. These studies, however, does not allow for the same complexity, diversity and dynamic nature of a tumor microenvironment [8].In addition, the use of in vivo humanized mice models arenot sufficient to address unavailability of human tissue donors, species incompatibility and human cell lineages which may be critical to investigate cancer progression and metastasis. Thus, the development of biomaterials as a functional reproduction of tissue/organ model through mimicry of cellular components and extracellular matrix is required [9].

The use of a 3D model are usually initiated by layering urothelial cells, fibroblasts and endothelial cells which are later grafted by bladder cancer, RT4 and T24 cell line, spheroids by using the hanging drop technique. As a result, the bladder cancer model can be used to assess drug responses and toxicological evaluation of anti-cancer therapies in 3D [8].

To date, a number of 3D cultures have been discovered. However, they are still unable to simulate the spatial distributions of oxygen, metabolites and signaling molecules of tissues. Therefore, more studies attempted to use stacks of papers with suspensions of cells in an extracellular matrix hydrogel in order to allow for an oxygen and nutrient gradient control in 3D, and thus allowing the analysis of molecular and genetic responses in different perfusion levels of the model. This approach results in generation of a proliferating outside layer and a hypoxia core with over expressed hypoxia-sensitive genes [10].

In a 3D culture system, several studies have shown that spheroid models of certain cancer types could affect the efficacy of the immunity. For instance, melanoma cells in spheroids are poor stimulators of cytokine release by Melan-A/MART-1 or gp100 melanoma differentiation antigen specific cytotoxic T lymphocyte (CTL) clones. Moreover, CTLs can only poorly infiltrate target cells in spheroids. Finally, spheroid cultured tumor cells are also resistant to NK cell-mediated killing in the absence of monoclonal antibodies and cytokine stimulation [11].

Engineering Biomaterials for Cancer Immunotherapy

Biomaterials as Scaffold

Many studies have been investigating bioscaffold in order to modulate cancer microenvironment, assisting the generation of beneficial immune responses. Multiple approaches exist to achieve this goal, although the most prominent ones can be classified as modulating immune cells maturation and modification of the immune microenvironment itself [12].

Yang et al. reported that while poly (lactic-co-glycolic) acid (PLGA)-based scaffolds are the most commonly used scaffold for in vivo control release applications, PLGA is generally known to be hydrophobic [13]. This is remedied by incorporating modified, functionalized multi-walled carbon nanotubes (F-MWCNT) into PLGA scaffolds, improving the hydrophilicity of PLGA scaffolds and rough environment that is requiredfor dendritic cells (DC) maturation. Thus, the incorporation of F-MWCNT allows the PLGA-scaffold structure to be retained in the longer term. Not only is the structure retained but the amount of captured DCs was also observed to be higher and slower to be released when compared to pure PLGA scaffolds.

Retaining property of F-MWCNT incorporated PLGA scaffold is also observed in another experiment—fucoidan was incorporated into self-assembling peptides (SAP) through non-covalent interactions with amino acids present on the surface of striated nanofibrils underpinning SAP fibrous matrix as described by Li et. al [14]. The same group aimed to present fucoidan, which consists of highly solublepolypeptide chains, constrained in a 3D scaffold to improve its bioavailability. The mixture succeeded in delivering the fucoidan as intended, providing a non-toxic and biocompatible environment for the fucoidan to exert its function as anti-inflammatory and apoptosis inducer.

The 3D scaffold is also used as an immune cell maturation platform and in the case of research by Delalat et al., includes human CD4+ and CD8+ T cells [15]. Of note, they utilized a medical grade

polycaprolactone (PCL) to capture anti-CD3 and anti-CD28 antibodies for T cells priming. Furthermore, the interaction of reversibly adhering CD4+ and CD8+ T cells to antibodies captured in 3D lattice fibers generated rapid induction of proliferative signals.However, there appeared to be a limit to the antibody concentration that could produce increasing benefits for T cell expansion. Another advantage of a 3D PCL lattice structure is the roughness of the surface, as observed by Yang et. al. [13]. Both studies mentioned the possibility of bioscaffold mimicking the natural environment of the thymus, in which T cells mature when they come in contact with cytokines, other immune cells, and even the surface of the thymus itself [13, 15].

Not only used to modulate the immune system, bioscaffold also exists to deliver engineered immune cells and their stimulatory molecules by means of being the loading vessel of said treatment which will then be implanted surgically inside the body of the subject [12]. Biomaterials have been used as delivery agents in several ways as will be discussed in the subsection below.

Biomaterials as a Delivery System

Biomaterials have shown many potentials as a carrier of antigens and adjuvants into the body. Generally, there are two ways for a vaccine to be brought to antigen presenting cells (APCs): passive and active targeting. Passive targeting refers to indirectly targeting the APCs by utilizing biomaterials to deliver antigens to the targeted site. In passive targeting, the biomaterials can interact with cell membrane, whereby itwill target the charged surfaces of nanoplatforms. Active targeting refers to when APCs are directly targeted by biomaterials that have DC receptors ligands. Specific receptor-ligand interaction targets of active targeting are moiety of nanoplatforms, small molecule ligand, peptide, aptamer, and antibody [16].The aim of both delivery methods is to enhance the immune response against particular molecular targets, including cancer cells.

Nanoparticle is a suitable candidate to be utilized in vaccines and immunotherapeutic strategies in cancer. Improved pharmacokinetic profile, targeted delivery, protection of antigen enzyme degradation and improved stability of encapsulated cargo are the potential benefits of utilizing nanoparticle as a carrier [17]. Nano-carriers are used to carry therapeutic agents such as vaccines that are loaded with the desired antigen to enhance immunogenicity [18]. Chemotherapeutic drugs like oxoplatin (OXA), gemcitabine (GEM), and doxorubicin may also be carried to cause immunogenic tumor cell death [19-20]. Similarly, various compounds such as beta tricalcium-phosphate and CpG Oligodeoxynucleotide (CpG ODN) may also produce the same effects [21-22]. Nano-carriers act like a vesicle that not only carry these therapeutic agents, but also transport these drugs to the desired sites. Several studies have been conducted to illustrate its increased efficacy wherebythe use of advanced PLGA-based nanoparticlehas been proven tosignificantly increase antitumor efficacy [23].There are various biomaterials used as nano-carriers. Some of the most common biomaterials used are PGLA, gold nanoparticles (AuNPs) and chitosan. The major obstacle to understanding the full potential of cancer vaccines is its low immunogenicity [17].

AuNPs are one of the biomaterials that have taken the interest of researchers; it is already well explored in biomedical imaging, drug delivery, diagnostic tests and tumor treatment. A study by Ma et al. showed that the use of AuNPs increased the anti-tumor efficacy compared to monoclonal antibody treatment only [24]. Moreover, they enhanced the power of intracellular delivery of antigen, and thus enhance the immune response by a significant amount. Fogli et al. reported that inorganic nanoparticles have a spontaneous tendency to decorate their surface with protein coronas (PC) coating, and when it is in biological media, to build a self-assembled nanocarrier [25]. Spontaneous formation of proteins coronas on the nanoparticles, in this case the nanoparticles used are silica and gold nanoparticles, gives a fast, easy and cost-effective dendritic cells maturation. Both nanoparticles are great candidatesas carriers in cancer immunotherapy as both can be efficiently endocytosed and have no toxic effect. Protein coronas are formed due to the high surface energy of nanoparticles. Thus, when they dispersed most of the proteins, nucleic acids and lipids will be adsorbed to the surface, resulting in the formation of a protein corona.

As previously discussed, the novel formulations of biomaterials are under development, whereby one of the most recent onesis microneedles. A study by Wang et al. proposed a novel way to deliver anti-PD-1 in melanoma. PD-1 is a ligand that is presentedto the tumor which will then bind to PD-1 receptors of the T cells, preventing

its activation [26]. Free anti-PD-1 was found to have a good efficacy; however, its high costs due to repeated dosage and emerging side effects due to the presence of antibodies in the systemic circulation remain to be solved. Hence, the development of microneedle patches made of biocompatible hyaluronic acid integrated with pH-sensitive dextran nanoparticles encapsulating anti-PD-1 and glucose oxidase. The glucose oxidase activity allows for a controlled release of nanoparticles due to pH-dependent dissociation of the microneedle in a three day period. The same group found an increased survival and a more controlled release of anti-PD-1 throughout three days in a B16F10 mouse melanoma model.

It is known that tumor-associated antigens (TAAs) have poor immunogenicity and insufficient tumor antigen uptake by the APCs [27]. As a result, Duan et al. created an antigen delivery system that is based on pH-responsive metal-organic frameworks or also known as MOFs. The focus would be to find a solution regarding how to efficiently deliver TAAs to APCs and maximize the cross-presentation to yield stronger responses. The metal-organic framework has been known to have high capacity, chemical and structure diversity, low cost and biodegradability; making it the one of the best candidate for a carrier. TAAs co-delivery system, pH-responsive MOFs and immunostimulatory, induce a strong immune response. The addition of CpG to the co-delivery system will further elicit a stronger response and specifically enhances the Th1 response.

Chitosan is a cationic polysaccharide that is mainly derived from exoskeletons of crustaceans and it has been used extensively as vaccine delivery [28]. Chitosan-based nanoparticles with surface decorated mannose nanoparticle (Man-CTS-NP) has demonstrated to be a potential vehicle for vaccine delivery as it has been proven that Man-CTS-NP inhibited B16 tumor growth significantly compared to PBS-administered controls [29]. N-dihydrogalactochitosan (GC), has the ability to stimulate dendritic cells (DCs), making it a promising in situ autologous cancer vaccine. In addition, GC is a novel immune activator that was originally prepared by attaching galactose molecules to the amino group of the chitosan, resulting in regression of treated tumor and distant untreated metastasis [28].

PLGA-based nano-particles (PLGA NPs) have been studied comprehensively for the development of Ag vaccine. PLGA NPs are designed to envelop the Ag and the adjuvant, either inside the NP or on the surface. PLGA-based -CpG-ODN-coated tumor antigen nanoparticles are able to inhibit cancer cell growth, proliferation, and also promotes cell death [17]. CpG ODNs are successfully utilized as adjuvants to enhance anti-tumor immune defenses. However, the adverse effects of repeated CpG administration include pain at the injection site and frequent headaches. Nevertheless, PLGA-based-CpG-ODN-coated tumor antigen nanoparticles have the ability to promote the activation and maturation of dendritic cells, attenuate tumor growth and angiogenesis, and enhances the cytotoxic T lymphocytes function.

Biomaterials as Immunomodulatory Adjuvant

Antigen-based cancer immunotherapy relies on immunostimulatory molecules (adjuvant) for antigen uptake of dendritic cells prior to their localization and antigen cross-presentation to CD8+ T cell [30]. Combined inorganic biomaterials might act indirectly to the tumor site as an adjuvant through stimulation and modulation of various immune cells.

In the perspective of nanomedicine, biomaterials could be engineered as drug carriers that are combined with antibodies or adjuvant components in the conditions whereby encapsulated materials are incapable of penetrating into the immune cell. The utilization of polymer-based carrier materials such PLGA-based nano-particles had been designed to allow the penetration of adjuvant component into dendritic cells (DC). The first penetrated material is polyinosinic-polycytidylic acid (poly I:C) that promotes DC maturation and generates innate and adaptive immune responses through its interaction with Toll-like receptor 3 (TLR3). The second penetrated material is ovalbumin (OVA) as the antigen model [23]. Another example is lipid-based carrier in cytoplasmic delivery system of exogenous antigen towards DC to induce antigen-specific CTLs, which is mostly applied in viral fusogenic protein-incorporated liposomes [31]. A study by Wang et al. utilized tricalcium phosphate crystal (TPC) as an immunopotentiating adjuvant for hydrothermal extract of Human Tubercle Bacillus (HTB) [32]. TCP acts in delivery system by two ways: one as a bodily constituent based carrier for HTB and the second one as reservoir of biologically active elements such as Zn and Mg. Furthermore, the same group stated that HTB has been clinically

used to recover leukocytes of cancer patients post-radiation therapy.

Generally, many existing polymers have poor protein encapsulation, suboptimal dosing characteristics, and limited stability. Thus, a self-assembling nanogels that contain poly(hydroxyethyl methacrylate) (pHEMA) backbone with functionalized pyridine as hydrophobic side chain was developed [30]. These nanogels were applied as vaccines by encapsulating it withpurified tumor-associated antigen (TAA). In a further study and application, Yata et al. demonstrated a novel technology on DNA preparation through the self-assembly of nanostructured DNA and DNA hydrogels that have proven to be useful as a novel vaccine adjuvant, with their advantages, such as: safety injectability, biodegradability, tolerability, ability to stimulate the innate immune system and ability to deliver potential antigens to antigen presenting cells [33].

In another study, a sophisticated approach of nanovaccine has been developed by Liang and associates in the form of liposome-coated gold nanocages (Lip-AuNCs) that are modified with aCD11c for DCs targeting delivery of adjuvant monophosphoryl lipid A (MPLA) and melanoma antigen peptide derived from tyrosinase-related protein 2 [34].

Biomaterials for Immune Cells Engineering

Biomaterials have been used in the rapid expansion of T cells. Fadel et al. utilized carbon nanotubes for its high surface area and ability to be bundled [35]. Thus, cytokines and a number of T cell antigens were attached to the nanotube.It was shown that this nanotubewas able to rapidly activate and expand the T cells in vitro.

One of the formulations oftenseen in immune cell engineering is the use of lipid-based liposomes to introduce cytokines or other related molecules in order to aid immune cells. A study by Huang and associates has successfully programmed T cells to retain homing receptors for lymphoma cells and attaches it with a nanocapsule [36]. The nanocapsule is loaded with a topoisomerase I poison, SN-38, which initially has very poor pharmacokinetics. This delivery system successfully reduced tumor burden by two weeks of treatments. Another study also utilized the free thiol groups of T cells but attaches a nanoparticle containing NSC-87877, an inhibitor of Shp1 and Shp2, which could down regulate T cell function [37].

Dendritic cell activation can also be a target for biomaterial usage. For instance, dendritic cells have also been activated by either cationic liposomes and PLGA nanoparticles [38].

In another study, nanoparticles decorated with cell penetrating peptides are loaded with IL-2 and GM-CSF in order to be taken up by Lewis lung carcinoma cell line. The cancer cells are then inactivated and injected to the tissue. The cancer cells which are full of IL-2 and GM-CSF will recruit more DC cells,and thus induces a stronger Tcell activation for the tumor-associated antigens of the inactivated cells [29].

Future Considerations

The use of biomaterials is beneficial in many aspects. For instance, the use of biomaterial as a vector could increase the specificity of its payload to its intended destination. As an example, several formulations of biomaterial could induce payload release in lower pH such as those found in cancer cells. A liposome formulated cell bound to Tlymphocytes could also be considered in the future for antigen-specific delivery of payload.

These increasingly specific formulations will then lead to the reduction of side effects of cancer treatments. Furthermore, biomaterials could open up the use of many drugs with poor pharmacokinetics. As drugs are encased in biomaterials, there will be significantly less free drug in the systemic circulation and thereby reduce non-target bindings and side effects.

Biomaterials also offer a slower and controlled release of chemotherapeutic agents which implicates a lower cost and increased convenience not having to constantly take treatment. A slower and controlled release, as was demonstrated through the use of microneedles, also eases the administration of chemotherapeutic agents.

One of the best features of biomaterials lies in its versatility as the same formulation of liposomes could be loaded or decorated with a huge variety of therapeutic compounds. Furthermore, with increased understanding in cancer immunology, it is expected to see various developments in biomaterials built as a treatment modality as was demonstrated in the whole cell cancer vaccine. In the near future, biomaterials could be paired with a wide array of immune cell-based cancer therapy. The ability of biomaterials to introduce and engineer immune cells in vivo and in vitro has merely just scratched the surface.

One of the pitfalls of using biomaterials is the lack of studies for its off-target toxicity, especially regarding the use of biomaterials in certain approaches such as vaccines, cytokines, checkpoint blockages and cell therapies [3]. Its versatility causes another problem to rise: with scientists trying to conjugate this and that to a single vessel to increase efficacy and effectivity of biomaterial-based treatment, complications and adverse effects might occur as the different drugs contradict each other. Furthermore, there are still no clinical trials available.Finally, for biomaterials to develop, many different fields of expertise, ranging from bio-engineers to immunologists to oncologists, are required to join forces.

CONCLUSION

Biomaterials are the next step in cancer immunotherapy by acting as a scaffold, a delivery system, an immunomodulator or activating cell-based therapies. The field of biomaterials is still not applicable yet with only studies on a preclinical level. However, with the versatility that is presented by biomaterials, the use of biomaterials for cancer therapeutics is very promising. Finally, more studies on the adverse effects of off-site bindings should also be studied and relevant laws and rules on the topic should be made for biomaterials to develop even further.

ACKNOWLEDGEMENTS

The authors are grateful to School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia for the financial funding.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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