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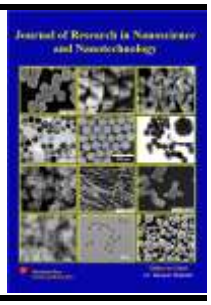

Investigation of Advanced Nanoscale Biomaterials as Immune Modulators for Therapeutic Applications

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ABSTRACT

Immunomodulatory agents play a crucial role in drug delivery by modulating the immune system's response to therapeutic agents, thereby enhancing treatment efficacy and safety. These agents can either stimulate the immune system to improve drug effectiveness, particularly in cancer and infectious diseases, or suppress it to prevent adverse reactions in conditions like organ transplantation and autoimmune diseases. The integration of immunomodulatory agents into drug delivery systems (DDS) enhances drug targeting, controls release, and optimizes pharmacokinetics. Advanced carriers such as nanoparticles and liposomes are employed to precisely deliver these agents, aligning with personalized medicine approaches to tailor treatments based on individual immune profiles. Despite their potential, challenges such as balancing immune modulation and addressing safety concerns remain. Ongoing research is focused on developing innovative DDS, improving targeting strategies, and identifying new immunomodulatory compounds to address these challenges. This abstract provides an overview of the role and impact of immunomodulatory agents in drug delivery systems and highlights the current trends and future directions in this evolving field.

Keywords:
Immunomodulatory agents, Drug delivery systems, Immune response modulation, Targeted drug delivery, Nanoparticles and liposomes, Personalized medicine

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1. Introduction

The human immune system is a highly developed network of cells, tissues, and organs that work together to protect the body from possible threats by defending against external agents including bacteria, viruses, fungus, and other pathogens. [1] Innate and adaptive immunity are the two primary immune systems that control immunological responses. The innate immune system, which comprises physical barriers like the skin and cells that can quickly identify and react to foreign invaders

including neutrophils, monocytes, macrophages, complement cascade, and cytokines, offers immediate non-specific defense against a variety of infections. [2] In contrast, the adaptive immune system is more specialized, takes longer to establish a defense, and activates immune cells with particular functions, including T cells and B cells, which can identify and retain particular infections. The body can react effectively to the same infection because of the immunological memory and long-term protection offered by the adaptive immune system. In order to develop a successful defense against infection, different signaling molecules and cells communicate with one another through finely coordinated interactions between innate and adaptive immune responses. This partnership guarantees a strong and all-encompassing immunological response. Since biomaterials have special qualities that allow them to interact with biological systems, they have been used in many medical fields, such as medication delivery systems, medical implants, and tissue engineering. When biomaterials are inserted, they frequently cause an inflammatory response known as a foreign body reaction (FBR). This reaction activates the immune system and can affect how well implanted materials function and integrate. In order to develop biomaterials for effective implantation and long-term functionality, it is crucial to comprehend and manage FBR. [3] When biomaterials induce FBR, immune cells such as neutrophils, monocytes, and macrophages are drawn in. These cells then release different cytokines in reaction to foreign substances, starting an inflammatory cascade. To become foreign body giant cells (FBGCs), macrophages undergo differentiation within this inflammatory milieu. Persistent FBR may ultimately jeopardize the material's normal function and impede tissue repair by causing biomaterial deterioration or tissue fibrosis. Lipids, polymers, and inorganic materials are examples of biomaterials. These biomaterials' characteristics, such as size, shape, stiffness, charge, and surface chemical composition, influence the different immunomodulatory reactions they elicit. [4] Implanted biomaterials' physicochemical characteristics significantly affect several immune system functions, macrophage polarization, and inflammation levels. [5]

The incidence and mortality of cancer are rising, making it a serious global public health concern that endangers human health. [6] With the use of external interference with the immune system, immunotherapy enhances or restores the body's capacity to combat malignancies, thereby preventing, controlling, and ultimately curing cancer. Immunotherapy, which includes cancer vaccines, cytokines, immune checkpoint inhibitors (ICIs), and other treatments, has emerged as a viable alternative to standard therapy for a variety of malignant tumors. These treatments have demonstrated impressive clinical outcomes. [7] Immunotherapy has clearly shown benefits, however, there are still a number of problems that require immediate attention in clinical use. Immunological medications, such as monoclonal antibodies, are injected systemically as part of immunotherapy. However, this method fails to precisely target the lesions and instead spreads the medications throughout the body's tissues and organs, leading to a host of immunological-related adverse responses. [8, 9] Effective anti-tumor immunological drug development should focus on issues that can optimize the therapeutic effects, such as how to enhance the pharmacokinetics and in vivo distribution of the drugs, increase the intracellular drug accumulation and the specificity of the targeted cells, and lessen the systemic severe side-effects caused by the non-specific reactions of the drugs. As a result, emphasis is growing on the study and development of drug delivery systems (DDS). [10, 11]

DDS offers the benefits of regulating drug release, enhancing drug solubility, enhancing pharmacokinetics, and enhancing drug dispersion. It is based on different chemical or biomaterials as carriers for drug delivery, or it combines pharmaceuticals with ligands tailored to particular cells. [12, 13] Additionally, medications can be precisely delivered to the target region via surface-modifying drug carriers (such nanoparticles) with specific ligands, improving treatment efficacy and minimizing side effects. [14] Therefore, the combination of DDS with tumor immunotherapy can

effectively and accurately deliver immune medicines to targeted locations, leading to useful anti-tumor effects. [14] Professor Paul Ehrlich invented the idea of "magic bullets" in the early 1900s, using certain monoclonal antibodies and cytotoxic medicines to destroy tumor cells. Antibody-drug conjugates (ADCs) were introduced decades later. [15] Since pharmaceutical technology has advanced during the past few decades, numerous coupling medicines, liposomes, polymer nanoparticles, and extracellular vesicles have been employed in clinical settings. [16] illustrate the number of nanoparticles and coupling medicines that have been approved so far for the treatment of cancer. However, the majority are employed in the delivery of cytotoxic medications during chemotherapy. More research is being done on the use of poorly stabilized and patterned drugs (such as proteins, peptides, antibodies, and nucleic acids) for tumor immunotherapy due to the ongoing development of novel delivery platforms such as extracellular vesicles (EVs), biomimetic nanoparticles, virus-like particles (VLPs), hydrogels, etc. [17, 18] Ongoing advancements in delivery technology allow for multi-drug combinations in addition to safer and more controlled effective targeting of immunomodulators to the targeted tumor or immune cells.

2. Immunomodulatory Biomaterials: Medical Uses

Biomaterials play a significant role in controlling immune mechanisms and the immune system. They are utilized in a variety of medical sectors, including tissue engineering, tissue regeneration, and cancer treatment, to reduce inflammation and regulate immune responses. Several tactics have been used to raise implanted materials' general biocompatibility and effectiveness for use in medical applications. This section examines the application of immunomodulatory biomaterials in cancer treatment and tissue regeneration, highlighting its significance.

2.1. Tissue Engineering using Immunomodulation and Regenerative Biomaterials

The promotion of tissue regeneration through the manipulation of immune responses with the use of biomaterials involves two main methods: either the intrinsic im injected with ECM formed from mineralized fibroblasts, which facilitates the proliferation and promotes osteochondral differentiation of human periosteum-derived cells in vitro. [19] For bone restoration, it's critical to use extracellular matrix (ECM) as a covering to enhance the biological characteristics of synthetic materials. [20] Scaffolds, hydrogels, and films are just a few of the materials based on graphene (GBMs) that play a significant role in fracture healing by encouraging angiogenesis, ossification, and the production of new bone. In addition to directly promoting the growth and differentiation of BMSC and osteoblasts, GBMs modulate immune cell polarization, impact the inflammatory response, and control cytokine secretion—all of which are critical processes in the regeneration of bone tissue. Increased production of new bone can be attributed to GOx's ability to polarize macrophages, improve osteoblast differentiation, promote endothelial cell proliferation, and accelerate angiogenesis. [21] Furthermore, by blocking neutrophil adherence and recruitment, a GO film (GO/Ti) placed to the implant abutment surface reduces peri-implant inflammation and encourages bone cell adhesion and bone deposition. [22] When treating bone abnormalities, GBM can be utilized as a medication carrier to effectively load and gradually release IL-4, BMP-2, and baicalin to reduce inflammatory responses and encourage bone regeneration. To encourage osteoblast activity and speed up the mineralization of the matrix at the fracture site, a negative charge must be generated. This emphasizes how crucial piezoelectric stimulation is for controlling bone repair. [23] The ability of piezobiopolymers and piezobioceramics to induce stress raises bone metabolism. Piezo-bioceramics and biopolymers produce surface charges under external stress, just like bones do.

Effective fracture repair is promoted by the polarization of piezoelectric surfaces, which improves the osteogenic performance of native bone. [24]

2.1.2. Nerve tissue engineering

Tissue-engineered scaffolds are constructed with optimum biomechanical qualities to facilitate nerve realignment and functional recovery. These scaffolds are used as nerve grafting materials in the treatment of peripheral nerve injuries. [25] In models of peripheral nerve abnormalities, a wide variety of natural and synthetic biomaterials, including collagen, PCL, and PLLA, have been used to fabricate nerve grafts. [26] For instance, the longitudinal and chemotactic development of axons in vitro is guided by aligned PCL fiber conduits coated with a concentration gradient of nerve growth factor (NGF). Chemotaxis is a crucial process in wound healing, immunological responses, and neurovascular development because it controls cell movement through alterations in chemical gradients. These channels promote neuron regeneration by means of 19 amplified signaling pathways linked to axon traction. [26]

Put differently, the NGF gradient/aligned PCL fiber conduit offers a peripheral nerve defect repair option other than autologous nerve transplantation26. Peripheral nerve regeneration is further enhanced by the integration of 3D-printed aligned collagen hydrogels into poly(lactide-co-caprolactone) nerve-guide conduits. [19] Materials based on conductive graphitic can help neurons survive, encourage neurite outgrowth, and ease electrical signaling within cells. In neural networks, its intrinsic conductivity is useful for creating synaptic connections and sending messages. It's important to take into account how immune cells like macrophages contribute to peripheral nerve regeneration. [27] Upon peripheral nerve injury, macrophages are required to phagocytose debris and initiate anti-inflammatory immune responses to alleviate inflammation. [28] Excessive activation of the inflammatory response results in the formation of fibrous tissue at the site of damage. This fibrous tissue obstructs the penetration of the tissue engineering scaffold, impeding axon regeneration and upsetting the support of Schwann cells. Consequently, it is necessary to control the intricate inflammatory reaction linked to peripheral nerve damage. [29] GBMs can be used to a variety of materials and processes, such as films, foams, hydrogels, electrospun fibers, and 3D printing. These many forms are perfect resources for stimulating nerve growth and enabling restoration. [30] In order to support neurite outgrowth and angiogenesis, GBMs drive the proliferation of neuronal cells and guide stem cell differentiation. In addition, GBMs control inflammation and immune cell polarization, which affects the local immunological milieu and aids in brain tissue regeneration. [31] Graphene, for instance, causes the resident macrophages of the nervous system, known as microglia, to polarize toward an anti-inflammatory phenotype. This promotes neuronal differentiation and axon regeneration while inhibiting acute inflammatory responses in neural tissue. [32] In order to create a favorable immunological environment, encourage the proliferation and differentiation of cells associated to nerve tissue, and avoid problems like disconnection and persistent pain brought on by nerve tissue lesions, GBMs can therefore function as a carrier to modify the inflammatory milieu. [33]

2.1.3. Skin tissue engineering

Skin regeneration depends heavily on scaffolding; natural and synthetic scaffolds are thought to be the best ways to resolve problems related to the incorrect structure of skin tissue that has been restored. In addition, transitional scaffolds play a crucial role in the healing of skin wounds by promoting tissue remodeling via the interplay of many biological agents, including growth factors, anti-inflammatory agents, and antibacterial factors, all within a single structure. [34] Immune

regulation plays a key role in regenerative medicine, with an emphasis on eliciting the expression of the M2 macrophage phenotype. For example, dextran-isocyanatoethyl methacrylate-ethylamine-based bioabsorbable hydrogels have been demonstrated to enable skin regeneration and hair development in scar tissues, while also promoting the M2 macrophage phenotype and exhibiting great biocompatibility. Furthermore, adipose-derived MSCs and their extracellular matrix (ECM) are essential for skin tissue engineering because they enhance fibroblast proliferation, encourage vascularized regeneration, and have immunomodulatory effects. For instance, an ECM made from human umbilical cord blood MSCs showed enhanced recruitment of M2-type macrophages and noteworthy improvement of vascularized regeneration levels in a skin healing model. [35] The three-dimensional hybrid scaffold showed a fairly balanced effect on controlling inflammation in macrophages. It was made by cross-linking extracellular matrix (ECM) with type-I collagen in both pre-induced pluripotent stem-cell-derived fibroblast (pre-iPSF Coll scaffold) and post-induced pluripotent stem-cell-derived fibroblast (post-iPSF Coll scaffold) forms. Notably, the post-iPSF Coll scaffold causes diabetic foot ulcer skin-derived fibroblasts to react more strongly, which results in the release of proteins that help the ulcer skin heal, including as VEGF and anti-inflammatory substances. [36] Repair vectors formed from the extracellular matrix (ECM) derived from fibroblasts facilitate vascularized skin regeneration. [37] Different GBMs have also been used to treat skin wounds, speeding up the healing process by stimulating angiogenesis and modifying the matrix by immune system modulation. [38] In 3D human skin models, GOx inhibits macrophages' production of proinflammatory cytokines and encourages the growth of normal skin tissue architectures. Additionally, GOx promotes the recruitment of a sizable number of neutrophils and has antimicrobial properties that hasten the healing of wounds. [39] When kynnipin is cross-linked with GOx-doped adipose-derived stem cell-derived extracellular matrix sponges, biocompatible and biodegradable materials are produced. These sponges have the potential to be sturdy scaffolding for healing wounds on the skin. [40] For example, combining human lung fibroblast-derived extracellular matrix (ECM) with PVA hydrogel to form a full-layer scaffold for skin restoration produced a large amount of human fibroblast-derived matrix in variables related to vascular regeneration. Composite scaffolds containing human BMSCs were implanted into skin defects in in vivo investigations, and the results showed superior performance in terms of wound healing rate, skin adhesion structure, collagen remodeling, and new blood vessel size. [41]

2.2. Immunomodulation for Cancer Immunotherapy

A promising tactic for boosting a patient's immune system to combat cancer is cancer immunotherapy. Unlike traditional chemotherapy or radiation therapy, cancer immunotherapy uses activated immune cells to recognize and target specific tumor cells, which may lessen the side effects often connected to conventional treatments. [42] Activated immune cells are used in cancer immunotherapy to identify and attack specific tumor cells. This strategy includes adoptive cell therapies such cancer vaccine therapy, immune checkpoint inhibition, TCR-engineered T cell therapy, chimeric antigen receptor (CAR) T cell therapy, and CAR-NK cell therapy. [43] Tumor microenvironment immunosuppression and immunological tolerance prevent the immune system from being the only means of tumor eradication. For instance, Treg cells operate on anti-cytotoxic-T-lymphocyte antigen 4 to reduce the antitumor efficacy of T cells. The antitumor immune response is suppressed by T cells' expression of programmed cell death ligand 1 and programmed cell death protein-1. [44] T cell penetration into tumor locations is often limited by the immunosuppressive tumor microenvironment, which is impacted by immune system-suppressed cells or cytokines, which hinders the cytotoxic efficacy of T cells. [45] In conclusion, immunotherapy may be ineffective if one

or more phases of the cancer immune cycle are disrupted. The importance of biomaterials in the development of cancer immunotherapy is emphasized in this section. Various biomaterials have been developed with the express aim of improving adoptive cell therapy efficacy, controlling the release of antigens to extend their presence, and optimizing anti-tumor immunotherapy by targeting lymph nodes with precision delivery. These developments have improved and expanded the efficacy of several cancer immunotherapy approaches.

2.2.1. Advanced drug delivery system

The toxicity and side effects of conventional chemotherapeutic treatments rise when they target both healthy and malignant cells, making treatment more difficult. The effectiveness of the treatment strategy may be further complicated by cancer cells' potential to become resistant to certain treatments. [46] The limitations of traditional chemotherapy have been addressed by the development of nanoparticles as a means of targeting cancer cells. Using smart nanocarriers for targeted drug delivery has a number of benefits, such as lowering drug dosage and frequency of application, enhancing drug stability, extending drug half-life, and resolving issues with current treatments, such as drug insolubility in water and lack of cell selectivity. [47] Nanomaterials possess intriguing physical, optical, and electronic characteristics that render them appropriate for use in several domains, specifically bionanomedicine and nanotechnology, which comprise the meticulous creation of functioning systems at the molecular level. Drug delivery has reached a previously unheard-of degree of sophistication thanks to the unique physicochemical characteristics of nanomaterials, which have facilitated the development of sophisticated multifunctional smart nanocarriers. [48] Numerous nanocarriers have been employed in medicine, imaging, and diagnostics, such as carbon nanotubes, polymer micelles, polymer nanoparticles, dendrimers, quantum dots, and quantum dots. Synthetic multifunctional nanocarriers are intended to minimize possible adverse effects while simultaneously recognizing, monitoring, and eliminating cancer cells within living organisms. These developments improve treatment efficacy by making it easier to track active targeting in real-time and precisely control medication release from nanocarriers. [49] A number of essential conditions must be met in order to produce the best smart nanocarriers for medication delivery. They should reduce negative effects on healthy cells and increase drug solubility and stability, which will lower treatment dosage and frequency. Drug nanocarriers also need to be immune system inert, not harmful to living things, and able to transport the required dosage of medication to the intended site for a prolonged length of time. [50] Numerous medical specialties, such as cancer treatment and vaccine development, can benefit from the use of these medication delivery systems. Clinical performance can be enhanced by carefully regulating the physicochemical characteristics of the biomaterials used in the delivery process. This includes the creation of controlled release systems for focused medication delivery. Personalized medicine has made significant strides thanks to the combination of biomaterials and drug delivery systems, which have made it possible to create precise and efficient treatments for a wide range of illnesses. Thus, there is still a need to investigate and create new biomaterials and delivery methods. [50]

2.2.2. Biomaterials for cancer immunotherapy

The field of immunotherapy has made significant strides in improving the clinical results of cancer treatment. By increasing therapeutic efficacy and reducing adverse effects, the incorporation of biomaterials into immunotherapy has recently demonstrated promise for the treatment of cancer. These biomaterials have clarified the fundamental processes of the immuno-editing process while

enhancing the effectiveness of immune checkpoint blockade medicines, cancer vaccines, and CAR T cells. [51] Biomaterials have been crucial in the advancement of cancer immunotherapy, offering significant contributions that have expanded and enhanced the efficacy of many cancer immunotherapy strategies. One of the most widely utilized multipurpose materials in biomedicine is polymer. Anti-tumor immunity is carried by a variety of polymer-based compounds, such as polyethyleneimine, chitosan, and PLGA.

Polymer-based materials play an important role in improving existing treatments such as chemotherapy, photodynamic therapy, radiotherapy, and gene editing by delivering agents with a variety of hydrophilic and hydrophobic properties while also promoting immunogenic cell death and anti-tumor immunity. [52] For example, using a light-activated prodrug of oxaliplatin in combination with the photosensitizer pheophorbide A and an indoleamine 2,3-dioxygenase 1 inhibitor effectively triggers an immune response and enhances Tc cell penetration into the tumor. [52]

Polymer nanoparticles with immunostimulatory properties modify macrophages linked to tumors. For instance, the development of pH-responsive polymer-based nanoparticles showed that these particles activate immunogenic T cells in the inflammatory tumor microenvironment when they are used to deliver cyclic guanosine monophosphate–adenosine monophosphate and the stimulator of interferon genes signaling in the tumor microenvironment and sentinel lymph nodes. The B16F10 mouse melanoma model's significant tumor growth inhibition served as confirmation of this. [53] In the context of immunotherapy, carbon-based materials like as nanotubes, GOx, quantum dots, and nanodiamonds could be used as drug delivery systems54. For instance, it has been shown that employing nanodiamonds to deliver immunostimulatory cytosine-phosphorothioateguanine oligonucleotides increases cytokine release. [54]

When it comes to drug delivery, hydrogels that form three-dimensional networks of crosslinked polymeric materials that range in size from nanoscale to macroscale are particularly adaptable. They can be used as immuno-modulators to boost antitumor immunity. [55] To increase the effectiveness of immunotherapies, nanoscale and microscale materials can be combined or encapsulated into larger hydrogel matrices. [56] For example, gel implants are capable of delivering tailored immune cells and stimulatory chemicals to treat malignancies that have been partially or totally removed locally. These results underline how hydrogels may be used in precision medicine to treat cancer. [56] Known as silica, silicon dioxide and its polymeric derivatives are a versatile family of materials with several advantages in therapeutic applications, including high loading capacity, great biocompatibility, gentle processing conditions, and easily adjustable surface functionalities. Furthermore, it is possible to design silica-based materials so that they completely biodegrade without losing their biological payloads, which increases the therapeutic efficacy of these materials. As a result, materials based on silica have shown tremendous promise as drug delivery vehicles. Numerous formulations have been created especially for use in tumor immunotherapy, including mesoporous silica microrods, hollow mesoporous silica nanospheres, mesoporous organosilica hollow spheres, and porous silica nanoparticles. [57] Biomaterials play crucial roles in various facets of cancer immunotherapy, including vaccines, CAR T cell Biomaterials are essential to many aspects of cancer immunotherapy, such as immune checkpoint blockade-based tumor regulation, CAR T cell treatment, and vaccines. These varied biomaterials, which are purposefully made to boost antitumor immune responses, span from tiny molecules to viruses, bacteria, and even macroscale organic and inorganic particles. Investigating new biomaterials has great potential to advance immuno-oncology. These compounds can be tailored to target certain tissues or cells, allowing for precision immune regulation at low dosages to lower treatment toxicity and adverse effects. Furthermore, in order to optimize the design and application of biomaterials in the complex field of cancer immunotherapy, more research into

the nature, specificity, and selectivity of biomaterial-mediated intracellular responses will aid in the development and implementation of successful immunotherapeutic strategies.

3. Conclusion

The integration of advanced drug delivery systems (DDS) with cancer immunotherapy has significantly advanced the treatment of malignancies by offering targeted, effective strategies for tumor management. Historical approaches such as Ehrlich's "magic bullets" have evolved into sophisticated technologies that leverage nanoparticles, liposomes, and other innovative carriers to enhance the precision and efficacy of cancer therapies. These advancements address longstanding issues of drug delivery, such as poor solubility, limited stability, and non-specific toxicity, by providing controlled and targeted delivery to tumor sites. In the realm of cancer immunotherapy, the use of biomaterials has been transformative. The development of advanced DDS has allowed for more efficient delivery of therapeutic agents, including immune checkpoint inhibitors, CAR T cells, and cancer vaccines. These innovations have improved the targeting of drugs, reduced systemic side effects, and enhanced the overall therapeutic efficacy. Nanoparticles, in particular, offer several advantages, including the ability to target cancer cells specifically, improve drug stability, and overcome challenges associated with conventional therapies. Furthermore, biomaterials have demonstrated their potential in various other medical fields, such as tissue engineering and regenerative medicine. For instance, in nerve and skin tissue engineering, advanced biomaterials like graphene-based materials and hydrogels have shown promise in promoting tissue regeneration, modulating immune responses, and enhancing the healing process. Despite these advancements, challenges remain, particularly in managing the complex immune landscape of tumors and avoiding immune-related adverse effects. Continued research and development are essential to further refine these technologies, improve their safety and efficacy, and tailor treatments to individual patient profiles. In summary, the synergy between DDS and immunotherapy represents a significant leap forward in personalized medicine, offering more effective and targeted treatments for cancer and other diseases. Ongoing exploration of novel biomaterials and delivery systems will likely yield further breakthroughs, advancing the field of cancer immunotherapy and improving patient outcomes across a range of medical conditions.

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