The Potential of Biomaterial-Based Solutions in Cancer Research and Treatment

Hannah Abigail Boone*
*International Burch University,
Sarajevo, Bosnia and Herzegovina
hannah.boone@stu.ibu.edu.ba

Literature review

Abstract: *Cancer is a very troubling disease due to its unique morphological characteristics, capacity for drug resistance, and immunosuppressive abilities. Traditional methods used both for research of cancer and its subsequent treatment have fallen short of being able to accurately understand and ultimately defeat cancer within the body. Biomaterials present a unique solution to many problems associated with cancer. The use of biomaterials in cancer cell modeling has promoted a better understanding of tumor microenvironments. Biomaterials can also serve as drug and adjuvant carriers that are more likely to reach their target cancer cells. Many biomaterials also have standalone antitumor properties, and can also help in modulating the immune response, triggering various immune cells to attack cancerous cells. Naturally derived biomaterials include polysaccharides, lipids, polypeptides, vitamin E derivatives, and even plant extracts like curcumin. Biomaterial-based cancer treatments tend to have a longer-lasting and more dependable effect inside the body and can come in many different forms, from polymeric scaffolds to injectable nanoparticles.*

Keywords: Adjuvant therapy, biomaterials, cancer treatment, carrier, immunotherapy.

1. Introduction

One of the most terrifying diagnoses to receive is the diagnosis of having any kind of cancer. Cancer is a very complex disease, as it occurs after mutations in the DNA of the cell cause morphological mutations that fundamentally change the biology and biochemical processes of the cell [1]. Cancer cells have many notable hallmarks, including their ability to divide indefinitely, their tendency to rapidly undergo glycolysis to secrete lactate even in the presence of oxygen, angiogenesis, and decreased cell senescence and apoptosis [1], [2]. To make matters worse, cancer cells can masterfully disguise themselves from immune cells such as cytotoxic T lymphocytes (CTLs) and dendritic cells (DCs), and can even recruit cells such as T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs) to keep other immune cells from recognizing them as cancerous [3], [4], [5]. Additionally, aggregated cancer cells form tumors with complex microenvironments, a phenomenon still not completely understood by scientists [6]. The combination of these factors stipulates that cancer is an incredibly difficult disease to treat, and it is no surprise that it has been considered a death sentence in the past [2].

However, there is hope to both biochemically understand and successfully treat cancer. One stride made in this area is the paradigm shift in how cancer is viewed, as some researchers and pharmaceutical industries are choosing to see cancer as a chronic illness with potentially life-threatening complications, rather than a life-threatening disease in and of itself [2]. Furthermore, toxic chemotherapeutic and radiotherapeutic treatments are no longer the only options for cancer treatment. This is due to the exploration of biomaterials as drug carriers, anticancer therapeutics, and adjuvant treatments [3], [7]. Biomaterials are uniquely suited to treat cancer as they are biocompatible with normal as well as cancerous tissue, allowing them to get close to their target cells, which is something that direct drug injections are often unable to do [2], [8]. Additionally, biomaterials allow for in-depth 3D modeling of cancerous tumors and microenvironments, which has led to a deeper understanding of cancer and how to treat it [9]. This review aims to summarize how biomaterials can be used in both cancer research and treatment, in hopes of raising awareness of alternative solutions to conventional practices that are currently heavily relied upon and may ultimately harm patients.

2. The Cancer Microenvironment Challenge and Using Biomaterials as a Solution

One of the most challenging aspects of laboratory-based cancer research is the accurate modeling of cancer cells and metastasizing tumors. Cancer drug screening experiments have often been conducted using standard 2D cell culture for many years, which has fallen short of delivering a successful picture of how cancer drugs will affect tumors inside an *in vivo* setting [10]. The main limitations of 2D cell culture for cancer drug screening lie in the inadequate physiological and biological complexity of these systems, as well as a shortage of environmental factors that are present in a tumor, such as supporting secondary cell types and extracellular matrix (ECM) proteins [8]. For cancer cells to be properly understood and screened for therapies, a proper tumor microenvironment (SME) must be created [10]. TMEs can be cultured using various biomaterials and tissue engineering techniques [9]. There are two considerations to take into account when studying the TME: the physical and the chemical cues which indicate cancer and its subsequent drug resistance [10].

Physical cues are all indications of a tumor's physical ability to resist cancer drugs. The first cue is just the physical barrier presented by the tumor, which can increase drug resistance by simply keeping active substances away from the tumor core [10]. One of the most important physical cues is the structure of cancer's ECM [9]. The specific ECM around a cluster of cancer cells or tumors can contribute to cancer drug resistance because the ECM creates an environment that isolates the cancer cells from substances that might be harmful to them [6], [11]. ECM produced by cancer cells can undergo a process known as matrix stiffening, where collagen-

modifying enzymes such as proline hydroxylase, lysyl oxidase (LOX), and lysine hydroxylase cause the ECM to remodel itself to become harder; it is often an indicator of cancer progression [2]. The ECM can also secrete substances to make cancer cells more adhesive and can also activate anti-apoptotic signals [6], [10]. Additionally, TMEs inside the ECM produce biochemical cues, which include responses to hypoxia, where they may stop proliferating but can still withstand cytotoxic agents [8]. They can also make different changes with regards to pH, which translates to resistance in the form of ion trapping, efflux pumps, and resistance to acidic pH [10]. Additionally, the ability of tumors to interact with other cells outside the TME can trigger immune-suppressive responses for immune cells and anti-apoptotic responses within cancer cells [4], [10].

Many of these factors involved in TMEs cannot be properly simulated using standard 2D culturing. Fortunately, several methods for cancer cell culturing using biofilm-based 3D techniques exist [9]. Biomaterial-based research for cancer modeling is currently primarily conducted with synthetic polymers, such as polyethyleneimine (PEI) and polyethylene glycol (PEG), which researchers have begun using for the design of "intelligent" biomaterials to simulate the growth conditions of cancer cells, including spheroid formation techniques, 3D bioprinting, and organ-on-chips [2]. Polymeric scaffolds can be used to model the unique ECM environment present around cancer cells discussed previously [10]. Another technique under exploration is injection molding, where a mixture of cells containing some sort of naturally derived or synthetic cross-linking polymer, such as hydrogel or collagen, is injected into a highly detailed and specific mold [2], [8]. Microfluidic cell culture systems, which allow the manipulation of incredibly minuscule amounts of fluid (down to the nanoliter) can also be used to shed insight into cancer biology [10]. Additionally, bioprinting can be used to create specific cancer cell systems for drug testing [2]. Continued research into the use of biomaterials for 3D modeling of cancer cells and their TMEs could even shed light onto the more elusive concepts of cancer growth, such as immune response and microbiome affectation, as well as how cancer cells can alter their surrounding environments to ensure their survival [6].

3. Cancer Treatment Using Naturally Derived Biomaterials

Biomaterial-based cancer treatment can act against tumors and cancer cells in the following ways: by carrying a drug or adjuvant to the site of cancer cells or tumors, by having direct antitumoral properties, or by modulating the immune system and targeting it to attack cancer cells [2]. The reason biomaterials are increasingly explored as potential cancer treatments lies in the abilities of various biomaterials to better penetrate and attach to the TME of a tumor [2]. Biomaterial-based carriers can take the form of 3D structures such as scaffolds and conjugates generally formed by polymers of polysaccharides [12]. Injectable carriers such as liposomes, inorganic nanoparticles, or polypeptides can be injected into the body and then allowed to find their target [3]. While the biophysics and chemistry behind biomaterial carriers are, of course, complex in nature, the concept is fairly simple: a drug, nucleic acid sequence, adjuvant, or other anticancer substance is loaded onto a specific carrier, often labeled with receptors that will allow the carrier to bind to cancer cells [2], [3]. Once bound to the target cells, the carrier releases its contents. Some carriers that have adhesive properties, primarily polysaccharide-based carriers, can remain attached to a cluster of cancer cells, allowing a substance delivered to have a longer effect [2]. Certain biomaterial-based carriers have anticancer properties in and of themselves, such as certain polar lipids, polymers, and polysaccharides, and some have characteristics that make them initially compatible and therefore recognizable by cancer cells, such as in the case of hyaluronic acid [2], [8].

Since cancer cells are exceptional at evading immune response, an important utilization of biomaterials in cancer treatment lies in the realm of immunotherapy. Biomaterial-based immunotherapeutics can have a longer-lasting effect when treating cancer than simple injections

of chemotherapeutic drugs or radiotherapy [12]. There are multiple ways in which biomaterials can stimulate *in vivo* immune responses to cancer cells. Biomaterials containing both antigens and immune adjuvants can stimulate DCs and other antigen-presenting cells (APCs) that may have been inactivated by cancer cells [7], [13]. Another method for stimulating an immune response to cancer is by interfering with T cells whose receptors do not recognize cancer cells as pathogens due to inhibitory factors such as PD-1/PD-L1 and CTLA4 released by the cancer cells; by injecting an anti-PD-1/PD-L2 and CTLA4 antibodies, T cells can be reprogrammed to view cancer cells as targets [7]. Additionally, immune-stimulating cytokines such as interleukin-2 (IL-2) and interferon-alpha (IFN-alpha) can be coupled to a biomaterial carrier and injected to serve as an immune response adjuvant by stimulating the production and differentiation of CDLs [3]. Other adjuvants include toll-like receptor (TLR) agonists, pathogen-associated molecular pattern (PAMP) molecules, and damage-associated molecular pattern molecules (DAMP), all of which aid in activating both innate and adaptive immune response [4].

4. Types of Naturally Derived Biomaterials Used in Cancer Treatment and Research

For cancer research and treatment, it is often more cost-effective, efficient, and safe to use biomaterials naturally synthesized by algae, plants, animals, and in some cases even bacteria, as opposed to synthetic materials [8]. Some of the more commonly utilized biomaterials include polysaccharides such as chitosan, noted for its cytotoxic ability in certain breast cancer lines; hyaluronic acid, which is significantly present in tumors and can function as an effective drug/adjuvant carrier; alginate, which induces the release of proinflammatory cytokines from macrophages; or pectin, which can function as a drug carrier and has apoptotic-stimulating abilities [2], [8].

Polar lipids can also be used for cancer treatment, as their amphipathic structure allows them to carry various drugs that are either hydrophobic or hydrophilic [2]. Lipid-based nanomaterials can serve as carriers of antigens and immune adjuvants targeting DCs, to initiate a CTL response [3]. The use of lipid-based biomaterials and liposomes showed to have a significant effect on the immune system. One study sought to create a cancer vaccine by loading liposomes with a peptide specific to melanoma, TRP2, and a CpG-ODN immune adjuvant, and the vaccine was found to improve the survival of tumor-bearing mice [15]. Some lipids even have direct anticancer properties, as in the case with alkyl phospholipids (APLs) which have shown antineoplastic activity by interfering with lipid metabolism in cancer cells [2].

Other natural biomaterials such as polypeptides and vitamin derivates can also be used as both carriers and tumor antagonists. Polypeptides and peptide derivatives can also serve as drug and gene therapeutics carriers and are recognized for their significant biocompatibility and chemical reactivity, and certain polypeptides such as polylysine, polyarginine, polyhistidine, and polyglutamic acid have direct antitumoral or immunomodulatory activities [2]. The vitamin E derivate alpha-tocopherol-succinate (TOS) can be paired with polysaccharide carriers such as hyaluronic acid and chitosan to form micelles for the loading of hydrophobic drugs [2], [16].

TABLE 1. Specific Functions of Biomaterials in Cancer Treatment

Biomaterial	Type	Carrier	Directly Anti-Tumoral	Immunomodulatory
Alginate	Polysaccharide	✓		✓
Alkyl phospholipid	Lipid	✓	✓	
α-TOS	Vitamin E derivate	✓	✓	
Chitosan	Polysaccharide	✓		✓
Gold	Metal nanoparticle	✓	✓	✓
Hyaluronic Acid	Polysaccharide	✓		
Iron Oxide	Metal nanoparticle	✓	✓	✓
Liposomes	Lipid	✓		✓
Pectin	Polysaccharide	✓	✓	
Polyarginine	Polypeptide	✓	✓	
Polyglutamic acid	Polypeptide	✓		✓
Polyhistidine	Polypeptide	✓	✓	
Polylysine	Polypeptide	✓	✓	
Silica	Nanoparticle	✓		✓

5. Curcumin Nanoparticles

One very notable example of a plant-extract biomaterial used to treat different cancers is curcumin, from which nanoparticles are created and then usually loaded onto a separate biomaterial carrier to then target tumors and cancer cells. Curcumin, chemically known as diferuloylmethane, is a polyphenolic substance extracted from the plant *Curcuma longa*, colloquially known as turmeric and used as a spice and coloring agent worldwide [17], [18], [19]. It has also been used in traditional Indian (Ayurvedic) and traditional Chinese medicine (TCM) practices to treat inflammation caused by a wide variety of disorders [19]. Research has shown that it suppresses NF-κB activation, a pathway that normally stimulates inflammation in cancer cells [18], [20], [21]. Curcumin also can downregulate AP-1 and STAT-3 pathways, which effectively retards the growth of cancer cells [18], [22].

Several studies have been performed to test if curcumin nanoparticles could truly work as anticancer agents when coupled with carriers formed from various biomaterials, and the results show promise for curcumin's use in the future for cancer treatment. Chitosan-coupled curcumin nanoparticles showcased the prominent mucoadhesive ability and drug retention when used to treat mouth cancer [23]. Another study used a silk fibroin and a blend of silk fibroin and chitosan polymers to encapsulate curcumin nanoparticles, where silk fibroin carriers were found to be more efficient due to their greater entrapment efficiency [24]. Other studies showed the prominent activity of curcumin nanoparticles against triple-negative breast cancer (TNBC) cells

and drug-resistant human ovarian adenocarcinoma cells [25]. Perhaps one of the most surprisingly effective uses of curcumin nanoparticles is against pancreatic cancer, and phase II *in vivo* studies reported that some patients experienced tumor regression and increased life expectancy, albeit small [20]. Numerous studies using curcumin against colorectal cancer reported that a variety of different carriers could be used to effectively transmit curcumin into the cell, including liposomes, other lipid carriers, micelles made of polymers, gold particles, and nanogels [22].

6. Conclusion

Various biomaterials could provide effective solutions to the massive challenges presented by cancer. By using polymeric scaffolds, tissue engineering, and intelligent biomaterial solutions such as organs-on-chips and microfluidics, tumor models can show a much more in-depth picture of the complexity of cancer dynamics and microenvironments. Many biomaterials themselves present antitumor or immunomodulating capabilities, which is a significant benefit when researchers look to use biomaterials therapeutically, in addition to being able to function as carriers for other anticancer therapies. Researchers have already looked into many different types of natural biomaterials, and one area of potential future research could be to examine how anticancer properties of different biomaterials might interact with one another to optimize cancer treatments. Another excellent focus area for future research would be to examine what kinds of cancers different biomaterials work best against. The wealth of research available showing the efficacy of biomaterials in both in vitro and in vivo treatments lends a lot of hope to a future where safe, effective, and even low-cost solutions for cancer exist, and people no longer need to fear cancer as a death sentence.

Appendix 1. List of abbreviations

CTL - cytotoxic T lymphocyte
DC - dendritic cell
Treg - T regulatory cell
MDSC - myeloid-derived suppressor cell
TME - tumor microenvironment
ECM - extracellular matrix
LOX - lysyl oxidase
PEI - polyethyleneimine
PEG - polyethylene glycol
APC - antigen-presenting cell
IFN-alpha – interferon-alpha

TLR - toll-like receptor
PAMP - pathogen-associated molecular pattern
DAMP - damage-associated molecular pattern
BMDC - bone marrow-derived dendritic cell
TNF - tumor necrosis factor
CpG-ODN - CpG oligodeoxynucleotide
alpha-TOS - alpha-tocopherol-succinate

7. References

[1] M. Vander Heiden and R. DeBerardinis, "Understanding the Intersections between Metabolism and Cancer Biology", Cell, vol. 168, no. 4, pp. 657-669, 2017. Available: https://www.sciencedirect.com/science/article/pii/S009286741631755X.

[2] Kinam Park, Biomaterials for cancer therapeutics, 2nd ed. Cambridge: Woodhead Publishing, 2020, pp. 1-80.

[3] Alhallak, K., Sun, J., Muz, B., & Azab, A. K. (2020). Biomaterials for cancer immunotherapy. In Biomaterials for Cancer Therapeutics (pp. 499–526). Elsevier. https://doi.org/10.1016/B978-0-08-102983-1.00018-1

[4] Bisht, S., Feldmann, G., Soni, S., Ravi, R., Karikar, C., Maitra, A., & Maitra, A. (2007). Polymeric nanoparticle-encapsulated curcumin ('nanocurcumin'): A novel strategy for human cancer therapy. Journal of Nanobiotechnology, 5(1), 3. https://doi.org/10.1186/1477-3155-5-3

[5] Bonnans, C., Chou, J., & Werb, Z. (2014). Remodelling the extracellular matrix in development and disease. Nature Reviews Molecular Cell Biology, 15(12), 786–801. https://doi.org/10.1038/nrm3904

[6] Dhillon, N., Aggarwal, B. B., Newman, R. A., Wolff, R. A., Kunnumakkara, A. B., Abbruzzese, J. L., Ng, C. S., Badmaev, V., & Kurzrock, R. (2008). Phase II Trial of Curcumin in Patients with Advanced Pancreatic Cancer. Clinical Cancer Research, 14(14), 4491–4499. https://doi.org/10.1158/1078-0432.CCR-08-0024

[7] Emami, J., Rezazadeh, M., Rostami, M., Hassanzadeh, F., Sadeghi, H., Mostafavi, A., Minaiyan, M., & Lavasanifar, A. (2015). Co-delivery of paclitaxel and α -tocopherol succinate by novel chitosan-based polymeric micelles for improving micellar stability and efficacious combination therapy. Drug Development and Industrial Pharmacy, 41(7), 1137–1147. https://doi.org/10.3109/03639045.2014.935390

[8] Goldberg, M. S. (2015). Immunoengineering: How Nanotechnology Can Enhance Cancer Immunotherapy. Cell, 161(2), 201–204. https://doi.org/10.1016/j.cell.2015.03.037

[9] Gupta, V. (2009). Fabrication and characterization of silk fibroin-derived curcumin nanoparticles for cancer therapy. International Journal of Nanomedicine, 115. https://doi.org/10.2147/IJN.S5581

[10] Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of Cancer: The Next Generation. Cell, 144(5), 646–674. https://doi.org/10.1016/j.cell.2011.02.013

[11] Hao, S., Yan, Y., Ren, X., Xu, Y., Chen, L., & Zhang, H. (2015). Candesartan-graft-polyethyleneimine cationic micelles for effective co-delivery of drug and gene in anti-angiogenic lung cancer therapy. Biotechnology and Bioprocess Engineering, 20(3), 550–560. https://doi.org/10.1007/s12257-014-0858-y

[12] Jo, Y., Choi, N., Kim, K., Koo, H.-J., Choi, J., & Kim, H. N. (2018). Chemoresistance of Cancer Cells: Requirements of Tumor Microenvironment-mimicking In Vitro Models in Anti-Cancer Drug Development. Theranostics, 8(19), 5259–5275. https://doi.org/10.7150/thno.29098

[13] Kretlow, J. D., & Mikos, A. G. (2008). From material to tissue: Biomaterial development, scaffold fabrication, and tissue engineering. AIChE Journal, 54(12), 3048–3067. https://doi.org/10.1002/aic.11610

[14] Lai, C., Duan, S., Ye, F., Hou, X., Li, X., Zhao, J., Yu, X., Hu, Z., Tang, Z., Mo, F., Yang, X., & Lu, X. (2018). The enhanced antitumor-specific immune response with mannose- and CpG-ODN-coated liposomes delivering TRP2 peptide. Theranostics, 8(6), 1723–1739. https://doi.org/10.7150/thno.22056

[15] Mazzarino, L., Loch-Neckel, G., Bubniak, L. D. S., Mazzucco, S., Santos-Silva, M. C., Borsali, R., & Lemos-Senna, E. (2015). Curcumin-Loaded Chitosan-Coated Nanoparticles as a New Approach for the Local Treatment of Oral Cavity Cancer. Journal of Nanoscience and Nanotechnology, 15(1), 781–791. https://doi.org/10.1166/jnn.2015.9189

[16] Park, O., Yu, G., Jung, H., & Mok, H. (2017). Recent studies on micro-/nano-sized biomaterials for cancer immunotherapy. Journal of Pharmaceutical Investigation, 47(1), 11–18. https://doi.org/10.1007/s40005-016-0288-2

[17] Pradhan, S., Hassani, I., Clary, J. M., & Lipke, E. A. (2016). Polymeric Biomaterials for In Vitro Cancer Tissue Engineering and Drug Testing Applications. Tissue Engineering Part B: Reviews, 22(6), 470–484. https://doi.org/10.1089/ten.teb.2015.0567

[18] Singh, A., Brito, I., & Lammerding, J. (2018). Beyond Tissue Stiffness and Bioadhesivity: Advanced Biomaterials to Model Tumor Microenvironments and Drug Resistance. Trends in Cancer, 4(4), 281–291. https://doi.org/10.1016/j.trecan.2018.01.008

[19] Vander Heiden, M. G., & DeBerardinis, R. J. (2017). Understanding the Intersections between Metabolism and Cancer Biology. Cell, 168(4), 657–669. https://doi.org/10.1016/j.cell.2016.12.039

[20] Wang, C., Ye, Y., Hu, Q., Bellotti, A., & Gu, Z. (2017). Tailoring Biomaterials for Cancer Immunotherapy: Emerging Trends and Future Outlook. Advanced Materials, 29(29), 1606036. https://doi.org/10.1002/adma.201606036

[21] Wong, K. E., Ngai, S. C., Chan, K.-G., Lee, L.-H., Goh, B.-H., & Chuah, L.-H. (2019). Curcumin Nanoformulations for Colorectal Cancer: A Review. Frontiers in Pharmacology, 10, 152. https://doi.org/10.3389/fphar.2019.00152

[22] Xia, Y., Shen, S., & Verma, I. M. (2014). NF-κB, an Active Player in Human Cancers. Cancer Immunology Research, 2(9), 823–830. https://doi.org/10.1158/2326-6066.CIR-14-0112

[23] Yang, F., Shi, K., Jia, Y., Hao, Y., Peng, J., & Qian, Z. (2020). Advanced biomaterials for cancer immunotherapy. Acta Pharmacologica Sinica, 41(7), 911–927. https://doi.org/10.1038/s41401-020-0372-z

[24] D. Hutmacher, "Biomaterials offer cancer research the third dimension", Nature Materials, vol. 9, no. 2, pp. 90-93, 2010. Available: http://www.australianprostatecentre.org/files/dietmar-hutmacher-article_2.

[25] N. Vallianou, A. Evangelopoulos, N. Schizas and C. Kazazis, "Potential Anticancer Properties and Mechanisms of Action of Curcumin", Anticancer research, vol. 35, no. 2, pp. 645-651, 2021. Available: https://ar.iiarjournals.org/content/anticanres/35/2/645.full.pdf. [Accessed 28 May 2021].

[26] A. Chevallier, Encyclopedia of herbal medicine, 3rd ed. New York: Dorling Kindersley Ltd, 2016, pp. 1-98. Available: https://toniau.ac.ir/med/wp-content/uploads/docs/Book/%DA%A9%D8%AA%D8%A7%D8%A8/Encyclopedia%20Herbal%20Medicine.pdf

[27] Maya & Rajsekhar, Sharadha & Rajsekhar, Vardhini. (2015). Curcumin Nanoparticles: A Therapeutic Review. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 6. 2015-6.

Conflicts of Interest
The author declares no conflicts of interest.