

Strategy to modulate the tumor microenvironment using nanoparticles

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D – writing the article; E – critical revision of the article; F – final approval of the article

Polymers in Medicine, ISSN 0370-0747 (print), ISSN 2451-2699 (online)

Polim Med. 2019;49(2):63–66

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Funding sources

None declared

Conflict of interest

None declared

Acknowledgements

Authors are highly thankful to the Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University Greater Noida for providing library facilities.

Received on March 23, 2019

Reviewed on May 6, 2019

Accepted on September 15, 2019

Abstract

Tumors are considered as one of the deadliest diseases to affect the human body. Nowadays, nanoparticles, which are based on enhanced permeability and retention, have become prevalent in the treatment of tumors, as they have numerous advantages over conventional treatments of tumors. Recently, it has been reported that tumors are complex networks which comprise of neoplastic as well as non-neoplastic cells. The non-neoplastic cells, collectively called as stroma, assists in tumor progression and also in their survival. In this review, we summarize the strategies which help to modulate the tumor microenvironment in order to enhance nanoparticle delivery for the treatment of a tumor; this comprises of three main factors: improving tumor perfusion, facilitating nanoparticles extravasation and enhancing interstitial transport of nanoparticles. These strategies are beneficial due to the development of a new combination of therapeutic agents. The major role of the tumor microenvironment at the time of initiation and progression is to modify the fundamentals of tumor biology and also to improve molecular diagnostics and therapeutics. This review emphasizes the properties and characteristics of the tumor microenvironment that are utilized to develop drug delivery systems by nanotechnology, which aim to target tumor cells and tumor microenvironment.

Key words: nanoparticles, tumor stroma, tumor perfusion, tumor vessel normalization, tumor vessel disruption

Cite as

Agrawal H, Malviya R, Sharma PK. Strategy to modulate the tumor microenvironment using nanoparticles.

Polim Med. 2019;49(2):63–66. doi:10.17219/pim/112356

DOI

10.17219/pim/112356

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Introduction

A tumor is defined as a self-determining, sovereign disease of neoplastic cells. In recent days, the delivery of nanoparticle to cancerous cells has attracted vast attention in the field of the treatment of tumor.¹ Nanoparticles show advantages over drugs which is based on enhanced permeability and retention (EPR) effect. The basic properties of EPR are highly permeable tumor vessels that allows the permeability of particles which includes proteins, micelles, macromolecules, liposomes and other particles that are large enough to avoid renal clearance and causes enhanced retention of those extravagated particles.² Therefore, the main principle behind targeting with EPR effect that tumor targeted by nanoparticles delivery has gained huge success. Extensive literature discloses that EPR drug delivery was compromised by tumor microenvironment (TME).³ Tumor microenvironment is characterized by irregular vascular distribution, poor blood flow, elevated tumor interstitial fluid pressure, rich matrix, and abundant tumor stroma cells. The tumor microenvironment is an important part of tumor tissues, which functions as the soil for the seeds; it is the tumor microenvironment that is responsible for tumor cells proliferating, differentiating and promoting tumor growth. The TME consists of varieties of cells, namely, fibroblasts, myofibroblasts, adipocytes, immune cells, blood vasculature, lymphatic vasculature, and extracellular matrix.⁴ The tumor microenvironment and its cells have some significant irregularities, such as an acidic pH, hyperthermia, altered redox potential, up-regulated proteins, which can have an antitumor application, that is, by using stimulus-responsive nanopreparations.⁵ Thus, nanotechnology has become a developing field for stimulus-responsive nanopreparations in tumors, employing the altered tumor microenvironment to ease the accumulation of provided chemotherapy at the tumor site, which allows for the specific targeting of the tumor and also enables tumor microenvironment to achieve tumor growth inhibition.⁶ It is important to understand the basic difference between a tumor and cancer. In cancer the cellular growth is uncontrollable and it also spreads all over the body, but in the case of tumor, cancer develops when lump is formed inside the body due to abnormal cellular growth. A tumor may or may not develop into cancer. A tumor converts into cancer when it is malignant.

This literature will focus on the strategies applied to modulate the immune response as well as various aspects of TME targeted by nanoparticles. Extensive literature survey reflects that the tumor microenvironment plays a crucial role in the development, proliferation, and metastasis of tumors. Many of the conventional therapies designed to eradicate tumors fail because of the tumor microenvironment; therefore, nanoparticles take a lead into the properties of the tumor microenvironment.⁷ Different strategies are applied to improve the therapeutic benefits

of nanoparticles, which include employing active targeting nanoparticles, developing tumor-responsive drugs, optimizing the physiochemical parameters of nanoparticles, such as their shape, charge, and size. This review focuses on immune response modulating and also TME aspects targeted by nanoparticles delivery. The TME is framed by developing a tumor, and for tumor progression, both the cells, i.e., tumor cells as well as stroma cells, are provide benefit. Therefore, the logic for developing stroma cells at the tumor site has not been understood clearly. Stroma cells are basically a collection of cells which consist of immune cells, smooth muscle, vascular muscle, fibroblasts, endothelial, as well as extracellular matrix, along with the secreted molecules which behave in paracrine and auto-crine manners to enhance the survival of tumor cells.⁸ The growth of the tumor is revitalized by some of the growth factors and also by chemokines, which are produced by the immune cells in the stroma and also altered fibroblasts, which then engage more stromal cells. Consequently, the TME modification was considered as an important tool for nanomedicine delivery improvement. Hence, it is reported that delivery of the nanoparticles to the site of the tumor is based on two types of mechanism, namely active and passive mechanism. In a passive mechanism, nanoparticles, which have properties of long systemic circulation, have the ability to assemble in the interstitial space, where the selective collection is attained by enhanced permeability and retention effect. In the case of active mechanism, the nanoparticles are attached with molecular ligands, such as cell specific ligands, biological proteins, antibodies, peptides, etc. These ligands improve the cellular uptake of nanoparticles via receptor-mediated endocytosis.⁹⁻¹¹

Strategies to modulate tumor microenvironment

There are several strategies used for modulating tumor microenvironment to enhance the nanoparticles delivery for the treatment of tumor and they are divided into the following three categories: improving tumor perfusion, facilitating nanoparticles extravasation and enhancing interstitial transport of nanoparticles (Fig. 1).¹

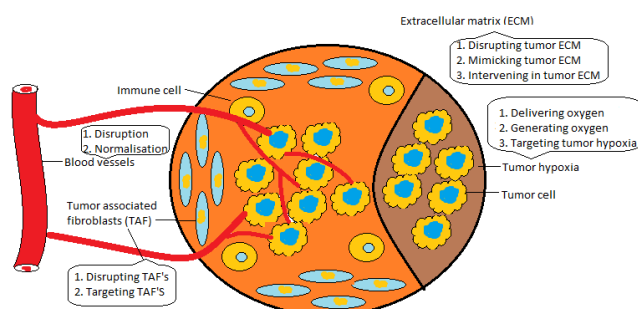


Fig. 1.

Tumor vessel normalization

The newly formed tumor vessels are always curvy and drippy, which allows nanoparticles extravasation, but, at the same time, this increases interstitial fluid pressure, which helps in preventing adequate blood flow of nanoparticles. The goal is to improve nanoparticle delivery for the treatment of a tumor; for this the vessels need to be normalized, which has been found to be an efficacious approach to improve nanoparticle delivery. During normalization of vessels, the abnormal phenotype of tumor vessels transforms into the phenotype, which seems to closely resemble functional normal vessels by mending the basement membrane and increasing coverage rate of pericytes and eventually decreases leakiness of vessel.¹² Hence, optimization in the tumor vessel structure can ultimately decrease the extravasation of fluid and also lowers interstitial fluid pressure and this cause's tumor blood flow to restore which can improve vascular transport of nanoparticles (Fig. 1). In this review, 4 strategies have been discussed for vessel normalization to improve nanoparticle delivery for the treatment of the tumor. The foremost strategy is capable of improving only the delivery of drugs which have a small molecular weight or drugs which have a small molecular weight compared to the nanoparticles, which range from 20 to 40 nm, but minimizes the delivery of nanoparticles which have a large molecular weight.¹³ This occurs because large nanoparticles reduce the endothelial gap of vessels of the tumor. The treatment for a tumor in the second strategy by nanoparticles is delivered during the normalization window. The treatment for a tumor in the second strategy by nanoparticles is delivered during the normalization window. Thirdly, it is necessary to prevent excessive elimination of tumor vessels; in order to achieve this appropriate dose of vascular normalizer is highly recommended. Lastly, this strategy is only applicable in the case of highly permeable tumors and not for desmoplastic tumors, because, as we know, vasculatures are highly constricted in the desmoplastic tumors.¹⁴

Tumor vessel disruption

In tumor tissues, vasoconstriction arbitrates via vasoconstrictive endothelin-1 (ET1) and also via its receptor, i.e., ETA, which is essential for maintaining the contractile tone of tumor vessels. The articulation level of ETA and ET1 for tumor vessels was found to be 13-fold and 5-fold elevated than normal vessels size.¹⁵ Therefore, a selective antagonist, i.e., BQ123, inhibits signaling between ET1 and ETA and tumor vessel dilation, and it also triggers a tumor-specific increase in blood flow. The increase in blood flow is caused by BQ123, which can improve the delivery of the free drug to tumors. Moreover, it was found that BQ123 can increase nanoparticle delivery for tumor treatment.¹⁶

Inflammatory mediators

Tumor necrosis factor alpha, VEGF, and nitric oxide (NO) donors¹⁷ are some of the inflammatory mediators which have the ability to enhance vascular permeability. This enhanced vascular permeability can be used to enhance the accumulation of nanoparticles in tumors higher than control group, i.e., 2 to 6-fold higher. After vascular permeability is enhanced, vasodilatation and blood flow need to improve. This improvement occurs by means of inflammatory mediators. These inflammatory mediators, which give a series of effect, can also participate in the elevation of interstitial fluid pressure against nanoparticles delivery.¹⁷ Hence, the accumulation of nanoparticles in tumor cells apparently depends on these factors.

Depletion of pericyte

In a desmoplastic tumor, pericytes coverage rates on endothelium were about 70% higher than in highly permeable tumors, which ultimately restricts the transvascular movement of nanoparticles into tumor interstitium. Therefore, certain strategies are being developed to reduce the coverage rate of pericytes of the endothelium by using a low dose of an LY36947 and TGF- β and also to increase size gaps between the endothelium. This can increase the therapeutic benefits of many drugs.¹⁸ In a literature review, therapeutic benefits of gemcitabine loaded liposomes delivered for pancreatic tumor and also Doxil-loaded liposomes for diffusion type gastric tumor have been reported.¹

Depletion of platelets

It is known that homeostasis is triggered by platelets, which play the primary role in thrombus formation. Apart from this role, platelets also contribute to tumor progression and metastasis. Additionally, tumor vascular homeostasis is also supported by platelets as well as the integrity of tumor vessels.¹⁹ Extensive studies have revealed that a reduced number of platelets causes severe blood flow at the tumor site and can also causes leakiness of tumor vasculature. A study has reported that, platelets reduction in thrombocytopenic mice increase efficiency of chemotherapy for breast cancer. Another study has found that TME responsive nanoparticles have the ability to deliver antibodies to deplete the selective platelet in tumor tissues; this was done to avoid bleeding in normal organs of the body.²⁰ Following this, vascular permeability was augmented and, as a result, nanoparticle delivery for tumor treatment was improved. It has been concluded that the depletion of platelets is a reliable means of augmenting transvascular delivery for treatment of tumors through nanoparticles.²¹

Physical stimulus


Physical stimulus includes radiation, which can improve nanoparticles delivery for tumor.²² A literature survey reveals that there are various mechanisms wherein radiation can regulate the growth of vascular endothelial factor, and this is regulated by activating the HIF1 factor, i.e., the hypoxia-inducible factor 1, and also by multiple mitogen-activated protein kinase-dependent pathways which enhance tumor vessel permeability.²³ Therefore, after an extensive literature survey, results have revealed that permeability of tumor vessels permeability of imaging-contrast agent with the molecular weight above 200 kDa was increased by 32.8% after irradiation. Moreover, radiation has the capacity to kill the tumor cells, which are sensitive in nature. It is concluded that the density of cells helped in diminishing compression stress of tumor cells and hence enhancing the blood flow of tumors, and the effect of radiation on tumors is dependent on the dose, time and tumor type.^{24,25}


Conclusions

Nanoparticle drug delivery has attracted considerable attention in the treatment of tumors. Nanoparticles in the tumor microenvironment provide a universal approach for anti-tumor therapy. Tumors are highly heterogeneous and, hence, growth is done in a complex microenvironment. The responsive peptide-base nanoformulations are also used for Improved Tumor Therapy. Tumor microenvironment consists of fibroblasts, immune cells, and extracellular matrix components. It is pivotal to formulate nanoparticles for a tumor which can easily adapt the tumor microenvironment and enhance the targeting of the drugs to the tumor cells. Recent advancements have been made in nanoparticle technology, allowing the development of tumor vasculature-targeted drug delivery, which can enhance the therapeutic efficacy of various anti-tumor medicines. Nanoparticles can directly affect the immune cells as well also their responses within the TME and they can also be functionalized to improve the particular subpopulations of immune cells, such as NK cells, DCs, and T cells.

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References

1. Zhang B, Hu Y, Pang Z. Modulating the tumor microenvironment to enhance tumor nanomedicine delivery. *Front Pharmacol*. 2017;8:1–16.
2. Allen TM, Cullis PR. Drug delivery systems: Entering the mainstream. *Science*. 2004;303(5665):1818–1822.
3. Barenholz YC. Doxil[®]—the first FDA-approved nano-drug: Lessons learned. *J Control Release*. 2012;160(2):117–134.
4. Albin A, Sporn MB. The tumor microenvironment as a target for chemoprevention. *Nat Rev Clin*. 2007;7(2):139.
5. Zhu L, Torchilin VP. Stimulus-responsive nanopreparations for tumor targeting. *Integr Biol*. 2013;5(1):96–107.
6. Cho K, Wang XU, Nie S, Shin DM. Therapeutic nanoparticles for drug delivery in tumor. *Clin Tumor Res*. 2008;14(5):1310–1316.
7. Siegler EL, Kim YJ, Wang P. Nanomedicine targeting the tumor microenvironment: Therapeutic strategies to inhibit angiogenesis, remodel matrix, and modulate immune responses. *J Cell Immunother*. 2016;2(2):69–78.
8. Roy A, Li SD. Modifying the tumor microenvironment using nanoparticle therapeutics. *Nanomed Nanobiotechnol*. 2016;8(6):891–908.
9. McMillin DW, Delmore J, Weisberg E, et al. Tumor cell-specific bioluminescence platform to identify stroma-induced changes to antitumor drug activity. *Nat Med*. 2010;16(4):483.
10. Teicher BA, Herman TS, Holden SA, et al. Tumor resistance to alkylating agents conferred by mechanisms operative only in vivo. *Science*. 1990;247(4949):1457–1461.
11. Fidler IJ, Wilmanns C, Staroselsky A, Radinsky R, Dong Z, Fan D. Modulation of tumor cell response to chemotherapy by the organ environment. *Tumor Metast Rev*. 1994;13(2):209–222.
12. Goel S, Duda DG, Xu L, Munn LL, Boucher Y, Fukumura D, Jain RK. Normalization of the vasculature for treatment of tumor and other diseases. *Physiol Rev*. 2011;91(3):1071–1121.
13. Chauhan VP, Stylianopoulos T, Martin JD, et al. Normalization of tumor blood vessels improves the delivery of nanomedicines in a size-dependent manner. *Nat Nanotech*. 2012;7(6):383–388.
14. Zhang B, Shi W, Jiang T, et al. Optimization of the tumor microenvironment and nanomedicine properties simultaneously to improve tumor therapy. *Oncotarget*. 2016;7(38):62607.
15. Sonveaux P, Dessy C, Martinive P, et al. Endothelin-1 is a critical mediator of myogenic tone in tumor arterioles: Implications for tumor treatment. *Tumor Res*. 2004;64(9):3209–3214.
16. Martinive P, De Wever J, Bouzin C, et al. Reversal of temporal and spatial heterogeneities in tumor perfusion identifies the tumor vascular tone as a tunable variable to improve drug delivery. *Mol Tumor Ther*. 2006;5(6):1620–1627.
17. Seki T, Fang J, Maeda H. Enhanced delivery of macromolecular antitumor drugs to tumors by nitroglycerin application. *Tumor Sci*. 2009;100(12):2426–2430.
18. Kano MR, Bae Y, Iwata C, Morishita Y, Yashiro M, Oka M. Improvement of cancer-targeting therapy, using nanocarriers for intractable solid tumors by inhibition of TGF-beta signaling. *Proc Natl Acad Sci U.S.A.* 2007;104:3460–3465.
19. Huang Y, Yuan J, Righi E, et al. Vascular normalizing doses of anti-angiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. *Proc Natl Acad Sci*. 2012;109(43):17561–17566.
20. von Maltzahn G, Park JH, Lin KY, et al. Nanoparticles that communicate in vivo to amplify tumour targeting. *Nat Mater*. 2011;10:545–552.
21. Demers M, Ho-Tin-Noé B, Schatzberg D, Yang JJ, Wagner DD. Increased efficacy of breast tumor chemotherapy in thrombocytopenic mice. *Tumor Res*. 2011;71(5):1540–1549.
22. Eikenes L, Tari M, Tufto I, Bruland OS, de Lange Davies C. Hyaluronidase induces a transcapillary pressure gradient and improves the distribution and uptake of liposomal doxorubicin (Caelyx[™]) in human osteosarcoma xenografts. *Br J Tumor*. 2005;93(1):81.
23. Moeller BJ, Cao Y, Li CY, Dewhirst MW. Radiation activates HIF-1 to regulate vascular radiosensitivity in tumors: role of reoxygenation, free radicals, and stress granules. *Tumor Cell*. 2004;5(5):429–441.
24. Stapleton S, Jaffray D, Milosevic M. Radiation effects on the tumor microenvironment: implications for nanomedicine delivery. *Adv Drug Deliv Rev*. 2016;109:119–130.
25. Qin H, Ding Y, Mujeeb A, Zhao Y, Nie G. Tumor microenvironment targeting and responsive peptide-based nanoformulations for improved tumor therapy. *Molecular Pharmacology*. 2017;92(3):219–231.