

Novel Insight into Blocking Cancer Metastasis by Biological Nano Confinement through Altering the Cancer Microenvironment

Abstract

Cancer is a devastating disease marked by a strong competitive capacity in energy and substance utilization in cancer cells compared to that in normal cells. This is partially due to the ability to adjust their metabolism in response to environmental changes. During the lifespan of a cancer cell, massive energy and substance demands are observed either in carcinogenesis, progress, or metastasis; however, the mechanisms involved are controversial and remain unclear. Understanding how cancer cells seize more energy and substances than normal cells is necessary for developing next-generation cancer therapy, including finding novel drug targets and designing drugs. Recent reports about mitochondrial hijack of cancer cells through self-assembled protein nanotubes connected with normal cells and graded messengers pool in the cytoplasm have evoked great interest. Considering the widely discussed nanodomain in physical and chemical areas in this perspective, biological nano confinement (BNC) was rationally discussed. We discuss various aspects such as the tendency of solid cancer cells to prioritize and utilize energy and substances at hypoxia while creating a lesser nutrition-supplying environment extra- and intra-cellularly, the paradox that chimeric antigen receptor T (CAR-T) therapies are effective in hematological cancers but less effective in solid tumors, and the fact that CAR-T adjuvant therapy with chemotherapy has synergetic enhancement effects. In addition, we concluded that developing novel inhibitors to depolymerize biological nanoconfinement is urgently needed.

Keywords: *Biological nano-confinement, Cancer, Metastasis, Energy and substances seizing, Chimeric antigen receptor T therapy*

Introduction

Cancer is responsible for the loss of hundreds of thousands of lives each year. Due to the disease heterogeneity and diversity, treatments are effective in only a subset of the patient population.¹ Surgery for cancer therapy has flourished with the advent of anesthesia and antisepsis, and radical surgery has long been seen as the primary approach to improve cure rates. Though the cooperation between trained experts including oncologists, radiologists, anesthetists, and nurses develop the surgical effect to a new height of minimally invasive and almost innocuous,² while the high rate of cancer relapse largely attenuated the cure efficacy. Radiotherapy has been the classical treatment measure for cancers and is advanced by the radiation-dose fractionation design.³ Also the advances in sensitizing tumors have greatly prompted the effects of radiotherapy.⁴ However, the multi-points occurrence and metastasis cancers remain vast and difficult to be

resolved. Cancer immunotherapy has dramatically changed the approach to cancer treatment by calibrating the host immune system to recognize and destroy cancer cells. However, the controversial efficacy of immunotherapy with identified adverse effects remains a large challenge for physicians.⁵ Additionally, this strategy seems to lack the potential for solid tumors. Even though, leukemia stem cells CAR T therapy still showed promising outcomes for leukemia patients, which may be associated with energy metabolism.⁶ Despite the specific cell surface antigens, self-renewal pathways, signaling pathways, and the epigenome-related cancer stem cell has been focused on in-depth,⁷⁻¹¹ the role of energy metabolism associated with these aspects remains obscure. To date, most patients need comprehensive treatment to tackle the resistant nature of cancer. While cancer metastasis may emerge at the very early stage of occurrence, clinical manifestations often lag. In recent decades, since technical developments have promoted early detection and local disease

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Access this article online

Website: www.cci-journal.org

DOI: [10.51847/0OzASxSCB1](https://doi.org/10.51847/0OzASxSCB1)

Quick Response Code:



How to cite this article: Zhao Z, Deng S, Wang Q, Jia C, Yang J. Novel Insight into Blocking Cancer Metastasis by Biological Nano Confinement Through Altering the Cancer Microenvironment. *Clin Cancer Investig J*. 2022;11(4):10-4.
<https://doi.org/10.51847/0OzASxSCB1>

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control, the 5-year survival rate for many patients with solid cancers has increased. However, some late relapses have always confused physicians; therefore, understanding the mechanisms of cancer metastasis is essential for therapy.¹² Although numerous studies have shown the possibility of blocking cancer metastasis theoretically, this is not the case in clinical practice. We investigated the possible reason: Are the signaling pathways regulating cancer metastasis not comprehensively revealed or is there any other way?

The hallmarks of cancer comprise six biological capabilities, which include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Among these hallmarks, genome instability plays an essential role.¹³ In addition, the reprogramming of energy metabolism and the avoidance of immune destruction make cancer cells reshape a brand new "tumor microenvironment", making it a bottleneck in cancer treatment, and also laying the foundation for the discovery of new cancer treatments.^{14, 15} Glycolysis has long been considered the major metabolic process for energy and anabolism in cancer cells, which implied that mitochondria play a key role in oncogenesis, hence the mitochondria have been regarded as promising targets for anticancer agents design.^{16, 17} This knowledge upturns our perceptions that cancer stems from epigenetic or genetic alterations;^{18, 19} and that aerobic glycolysis is the only path for energy supply to cancer cells.^{20, 21} Therefore, tumorigenesis and progression are very complex interactive processes.^{22, 23} Mitochondrial metabolism plays an inestimable and important role in tumorigenesis.^{24, 25}

Tumors are dynamic pseudoorgans, within which tumor cells interact with other non-tumor cells, forming a complex dynamic network of physiological environment. Therefore, tumor cells face many challenges and try to change their metabolic properties through this network connection to better maintain their malignant proliferation.²⁶ In general, glycolysis is upregulated in cancer cells, and oxidative phosphorylation (OXPHOS) expression should be down-regulated. But OXPHOS was found to be up-regulated in some cancers, even concurrent with active glycolysis.²⁷ In fact, the metabolic phenotype of cells in the tumor is heterogeneous. The metabolic rate of glucose, lactate, pyruvate, and hydroxybutyrate in cancer cells is much higher than that of normal cells. Therefore, the metabolic ecology of tumors is very complex. The heterogeneity and complexity of tumor cell metabolism enable it to not only use ATP as an energy source, but also maintain the reduction-oxidation balance, produce metabolic coupling with different cell populations, expand its energy source, and occupy an active dominant position in energy acquisition.²⁸

In any case, energy and essential substances required for anabolism are the necessary conditions for the development and proliferation of cells. While different cells in the same biological system can compete with each other for energy and essential substances through various routes, only those with

higher efficiency in energy and essential substance utilization develop preferentially. Cancer cells are in a relatively hypoxic environment with less energy supply; since cancer progression and metastasis need a large amount of energy and materials, this suggests that beyond the traditional energy supply and material intake theory, cancer cells must satisfy this demand through a hitherto unrecognized mechanism.

Results and Discussion

Nano-confinement is confinement in a nanosized region.²⁹ Commonly, when some active materials, such as conjugated polymers, metals, and even bio-active materials (protein, DNA, RNA, etc.) are confined at the nanoscale, they can exhibit unique nano-confined behavior that significantly differs from the behavior observed at the macroscale. Moreover, if this nano-confinement approach can be further expanded to other functional materials such as biomolecules, we believe that it can also provide a basis for the development and design of new strategies for cancer therapy in the terms of energy and substance utilization.³⁰⁻³²

Massive molecular studies implied that cancer cells own the priority on energy or substance up-taking over normal ones throughout their lifespan, yet we have not found any direct and more convincing clues to stand it. Of course, the above nano confinements are artificially designed to take advantage of their physico-chemical properties. Although the substances contained in this confinement have rich diversity, the shell of the confinement is still relatively simple and rigid, hence its utilization in biological systems is greatly restricted.³³ We believe that there must be a large number of various forms of such nanoconfined units existing in the biological system, which exert important functions in the process of tumorigenesis, progression, metastasis, and so on. Fortunately, very recent studies showed light on this mysterious phenomenon, which was called bio-nano-confinement (BNC).

A recent study reported that cancer cells can hijack the mitochondria from immune cells via physical nanotubes. When inhibiting the nanotube assembly machinery, these hijacks are significantly reduced.³⁴⁻³⁶ These nanotubes are the nano-confinement, which were constituted of special proteins and glycoproteins that were recruited by the signaling molecules from the extracellular space around the non-tumor cells under the control of cancers through trogocytosis action. However, these nanotubes were occasionally found due to their sparsely present having limited efficacy on mitochondria hijack (**Figure 1a**). This phenomenon involuntarily makes us consider the existence of other forms of nano confinements, such as those made up of the cytoplasm or other substances in the inter-cellular space, but they have not been fully discovered yet.

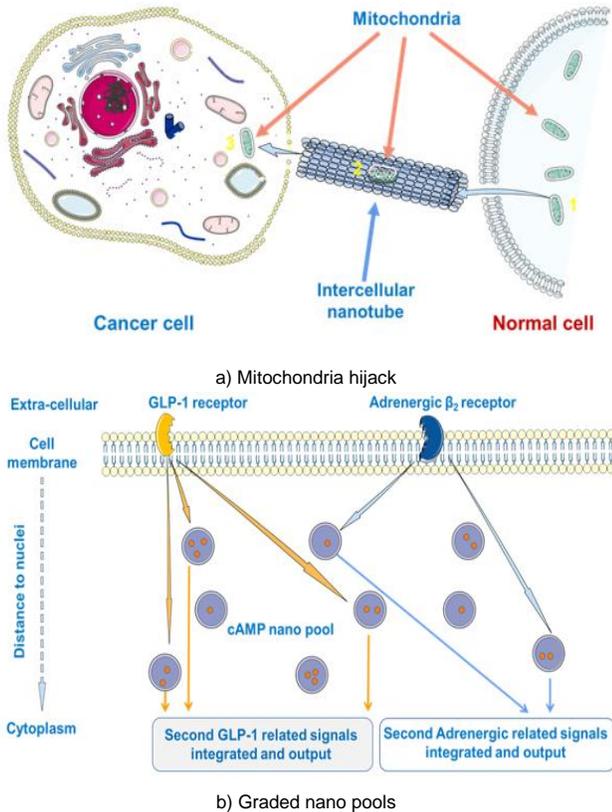


Figure 1. Distinguished from the traditional concept of energy and material utilization, here we conceptualize that biological nano confinement (BNC) is a novel path that facilitates cancer cell progression and metastasis. In this pathway, cancer cells prioritize energy use and substance uptake more than normal cells in a coexisting environment. a) Mitochondria hijack: Mitochondria of normal cells were hijacked by cancer cells through intercellular nanotubes constituted of proteins (possibly also of glucide, lipids, inorganic substances, and water). Among them, most special functional substances were probably recruited from normal cells by trogocytosis. This nanostructure is a kind of BNC. b) Concentration-graded messengers pools: In higher vertebrates, signal transduction usually occurs with a cascade model, rather than the simple stimulation-terminator one-step pathway. Membrane receptors are quite varied, while the second messengers are often limited in variety, with the same messengers usually responding to stimulation from different receptors. This is probably due to the special spatial distribution of concentration-graded messenger pools in the cytoplasm. Signals from various receptors trigger one or more different pools simultaneously, and the consequent response integrates and exerts the relevant bio-functions targeting extracellular stimulation.

The study that followed immediately confirmed our speculation. G protein-coupled receptors (GPCRs) relay extracellular stimuli into specific cellular functions. Cells express many different GPCRs, almost more than 200 types, but all these GPCRs target only a few second messengers, such as cAMP. It is unknown how cells distinguish between signals triggered by different GPCRs to orchestrate their complex functions. A recent study demonstrated that individual GPCRs signal via receptor-associated independent cAMP nanodomains (RAINs) that constitute self-sufficient, independent cell signaling units. The coexistence of many such RAINs allows a single cell to operate thousands of independent cellular signals simultaneously, rather than a simple “on/off” switch (**Figure 1b**). We firmly believe that such nanodomains are widely distributed in the cytoplasm and extracellular space in different forms and with a specific order, limiting different substances within them.³⁷⁻⁴¹

Moreover, as one of the star products of immunotherapy, CAR-T has shown great strength in blood cancer therapy. However, a significant portion still resists or relapses through immune evasion, which might be due to CAR T cell dysfunction, or a hostile tumor microenvironment. The intrinsic resistance mechanisms of cancer cells to CAR T cell therapy need to be illustrated promptly.⁴² For some anti-CD19 CAR T cell products applied to both acute lymphoblastic leukemia (ALL) and certain types of B cell lymphoma, a substantial number of patients had ameliorated due to the antigen loss or modulation, despite they owed to poor CAR T cell persistence and/or cancer cell resistance.⁴³ However, some scholars considered that the low effectiveness of CAR T cell therapy in the case of solid tumors was attributed to the immune effector cells exhaustion and their infiltration capacity abrogation resulting from the tumor microenvironment alteration. Moreover, they proposed meticulously-devised countertactics and combination therapies to maximize the therapeutic benefits of CAR-T therapies against solid tumors.⁴⁴ Previous studies suggested that CAR-T therapy has a drawback: T cells entering solid tumors may stop working because of the “T-cell failure” phenomenon.^{44, 45} Though targeting B7-H3 chimeric antigen receptor T cells has antitumor potential for therapy of non-small cell lung cancer (NSCLC), some formidable challenges remained due to the heterogeneous and immunosuppressive tumor microenvironment. Nanozymes exhibit merits modulating the immunosuppression of the tumor milieu by destroying its compact structure, then altering the immune-hostile cancer environment, resulting in enhanced activation and infiltration of B7-H3 CAR T cells.⁴⁶

To some extent, we can conclude that the inefficiency of CAR T therapy for solid tumors is partially resulting from the immune effector cells exhaustion and the alteration of the tumor microenvironment.^{47, 48} Whether T cell exhaustion or tumor microenvironment change seemed to be closely associated with BNCs by which exerting the energy and materials deprivation and signal transduction modulation.^{33, 37}

Furthermore, though chemotherapy has significant efficacy in hematological tumors, drug resistance is particularly obvious, often accompanied by severe adverse effects. While the combination with CAR T cell re-transfusion, this chemotherapy resistance was reduced. Why? Given the blood and lymphatic have higher fluidity, which is not conducive to the formation and maintenance of BNC, then the cancer cells lose priority in the competition of energy and material utilization with normal cells, and concurrent with the specific targeted CAR-T cells attacking, cancer cells become sensitive to therapeutic interventions, and ultimately showing good curative effect. On the other hand, CAR-T re-transfusion may potentially disturb the cancer cell signaling pathway, which regulates the trogocytosis to recruit components from T cells⁴⁹ to construct BNC, then made BNC collapse. As regards solid tumors, a relatively stable environment can facilitate the cancer cells to construct BNC, to some extent, making cancer cells resistant to drugs and feasible to proliferate (**Figure 1a**).

Conclusion

BNC is a novel concept and a promising target for cancer therapy, irrespective of the occurrence of solid tumors. However, the following problems need to be solved urgently:

1. Development of technologies for BNC characterization in biological systems.
2. Investigate the forms of BNC in biological systems.
3. Evaluate whether BNC interacts with known signaling pathways.
4. Investigate how homogeneous and heterogeneous BNC mediate energy and material uptake.
5. Explore the detailed mechanism by that BNC promotes CAR T therapy for hematological tumors.

Acknowledgments

None.

Conflict of interest

None.

Financial support

This work was supported by the National Natural Science Foundation of China (82071964, 72171170), Shanghai Municipal Health Commission (GWV-10.1-XK09), Shanghai Shenkang Center (SHDC2020CR2054B).

Ethics statement

None.

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