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Cellular Innate Biological Nano Confinements Control Cancer Metastasis Through Materials Seizing and Signaling Regulating

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Abstract

Cancer is a debilitating disease, causing millions of deaths annually throughout the world. Due to their adaptive ability to meet nutritional demands, cancer cells often utilize more energy than normal cells. In order to develop new strategies to treat cancer, it is necessary to understand the underlying mechanisms of energy metabolism, which is yet largely unknown. Recent studies have shown that cellular innate nanodomains are involved in cellular energy metabolism and anabolism and GPCRs signaling regulation, which have a direct effect on cell fate and functions. Therefore, harnessing cellular innate nanodomains may evoke significant therapeutic impact and shift the research focus from exogenous nanomaterials to cellular innate nanodomains, which will have great potential to develop a new treatment modality for cancer. Keeping these points in view, we briefly discuss the impact of cellular innate nanodomains and their potential for advancing cancer therapeutics, and propose the concept of innate biological nano confinements, which include any innate structural and functional nano domains both in extracellular and intracellular with spatial heterogeneity.

Keywords

Cellular nanodomains, energy metabolism, anabolism, metastasis, cancer

Abbreviations

GPCRs, G protein-coupled receptors; CAR T, chimeric antigen receptor T cells; FESEM, Field-emission scanning electron microscopy; FRET, Förster resonance energy transfer; cAMP, Cyclic adenosine monophosphate; TIRF, total internal reflection fluorescence; VAEM, variable angle epifluorescent microscopy; BNCs, biological nano confinements; GLP-1, glucagon-like peptide-1; iBNCs, innate biological nano confinements.

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Introduction

Harnessing the impact of cellular innate nanodomains has the potential to enable early detection and treatment of cancer, which is a leading cause of death worldwide, accounting for millions of deaths annually. Despite the successful treatment of cancer it remains a challenge, recent years have seen significant progress in identification, screening, and treatment modalities, which in turn increased the rate of survivability.[1] Cancer cells from early and later stages are generally characterized by malignant progression and metastasis, and thus understanding the cellular and molecular mechanisms of cancer metastasis is essential for efficient cancer therapeutics.[2] Metastasis commonly occurs several years prior to becoming a primary tumor and is responsible for cancer morbidity and mortality.[3] Though early detection of cancer metastasis remains a major challenge, advancements have been significantly achieved in recent years due to technological advances and is the most

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important strategy for controlling the spread of cancer. A previous study suggested that there is a possibility of blocking cancer metastasis,[4] but supportive clinical studies are limited. Now, a question arises whether signaling pathways regulating cancer metastasis are not comprehensively understood or if is there any other reason?

Cancer cells utilize more energy than normal cells due to their adaptive ability to change nutrient demands and have a diversity of energy production pathways. For developing efficient cancer therapy, it is necessary to understand the underlying mechanisms of energy usage which is surprising yet largely unknown. Both cancer and surrounding noncancerous cells, located in the same region, compete to fulfill their energy requirements through various routes. The most efficient cells in energy utilization can develop preferentially. Cancer cells are in a relatively hypoxic environment with decreased energy supply, indicating that their robust proliferation requires a supernatural capacity in capturing energy. Keeping these points in view, in this report, we explore the impact of cellular innate nanodomains and their potential for advancing cancer therapeutics.

Impact of Cellular Innate Nanodomains on Cancer Therapeutics

Cellular nanodomains are associated with energy metabolism related to cancer cell progression and metastasis.[5] For example, mitochondrial hijack of cancer cells by nanodomains of self-assembled proteins and concentration-graded messengers pool in the cytoplasm plays a key role in the progress of cancer. Therefore, cellular innate nanodomains is considered an emerging topic in molecular cell biology, in particular cancer biology, which helps develop the next generation of cancer therapy by regulating cellular energy and anabolism (Figure 1).

Though the nanodomains exhibit unique function and present a promising application in biological research (Table 1),[6] the heterogeneity of exogenous nanomaterials regarding their bioaffinity, biosafety, and effectiveness cannot be ignored.[7] In recent years, nanotechnology is becoming increasingly utilized in cancer therapeutics and it offers a new approach to early diagnosis and treatment.[8,9,10] For example, Luo et al., developed a controllable strategy to deliver interleukin-12 nanochaperone-engineered chimeric antigen receptor (CAR) T-cells, which has been wildly used to promote T-cell antitumor immune responses, to the tumor site.[11] This study demonstrated that the nanoparticles could be used for efficient and safe antitumor immunotherapy. Besides, there are numerous studies on exogenous nanomaterials, and some innate nanodomains have recently grabbed our attention due to their potential biological and biomedical applications.

A remarkable study reported that cancer cells can hijack the mitochondria from immune cells through physical nanotubes, transferring the mitochondria from immune cells to cancer cells, metabolically empowering the cancer cells and depleting the immune cells. A schematic of biological nano confinements elucidated by mitochondria hijack is shown in Figure 2A. Inhibition of nanotube machinery assembly can reduce this hijack significantly.[12] These nanotubes comprise special proteins and glycoproteins, but they are found sparingly.

Extracellular stimuli are relayed into the specific intracellular area by G-protein-coupled receptors (GPCRs), which have more than 200 types. Only a few second messengers like cAMP receive signals from GPCRs. The mechanism through which cells distinguish between signals triggered by different GPCRs to orchestrate their complex functions are largely unknown. A

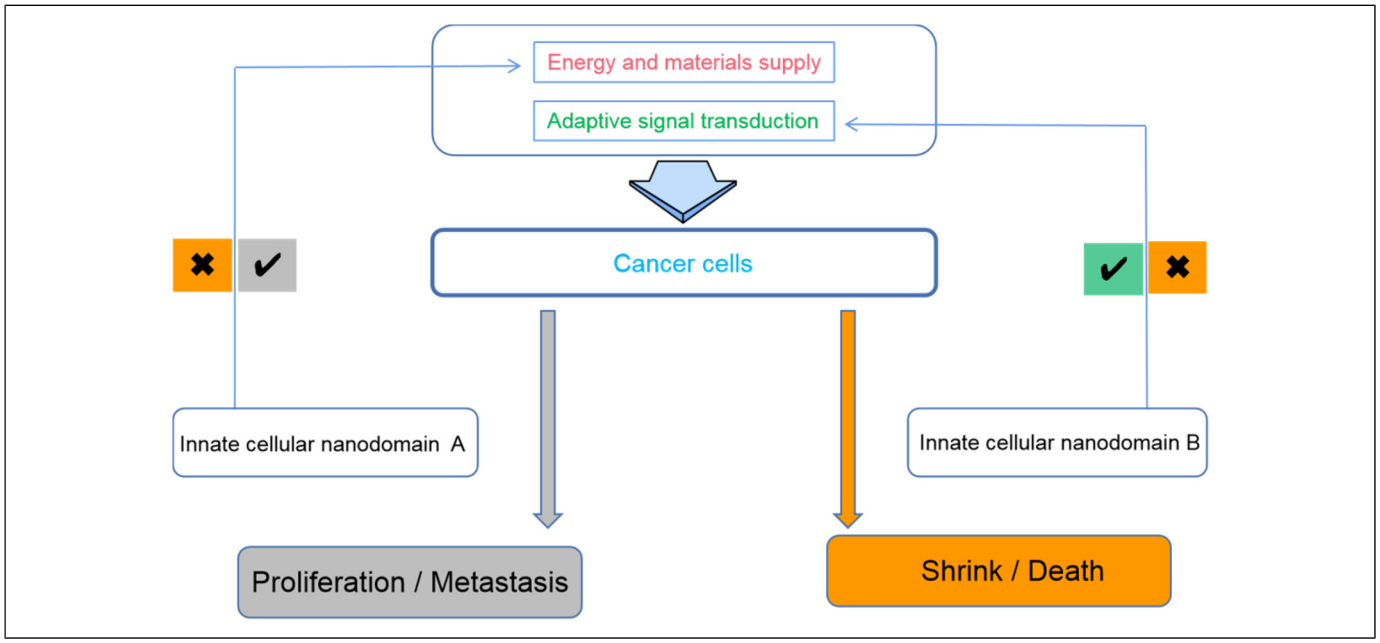

Figure 1 . Scheme of the impact of innate cellular nanodomains in cancer cells.

Table 1. Different Types of Innate Cellular Nanodomains

Nanodomains	Location	Scale (nm)	Detection methods	Function	Reference
Nano protein corona	Cytoplasm	<100	In-situ mass-spectrometry imaging	Proteostasis collapse, chaperone-mediated autophagy	5
Nanotubes	Extracellular	100-100	Field-emission scanning electron microscopy (FESEM)	Mitochondria trafficking	12
Nanopools	Cytoplasm	50	FRET-based cAMP biosensors, other ions detection	Messengers conservation	13
Nano-organization	Membrane	<100	Point scanning confocal microscopy, total internal reflection fluorescence (TIRF), variable angle epifluorescent microscopy (VAEM)	Cell nutrition and signaling	14
Nano-clustering	Active zones of neurons	100	Quantitative TIRF microscopy and step-wise photobleaching	Regulation of synaptic vesicle docking and fusion	15

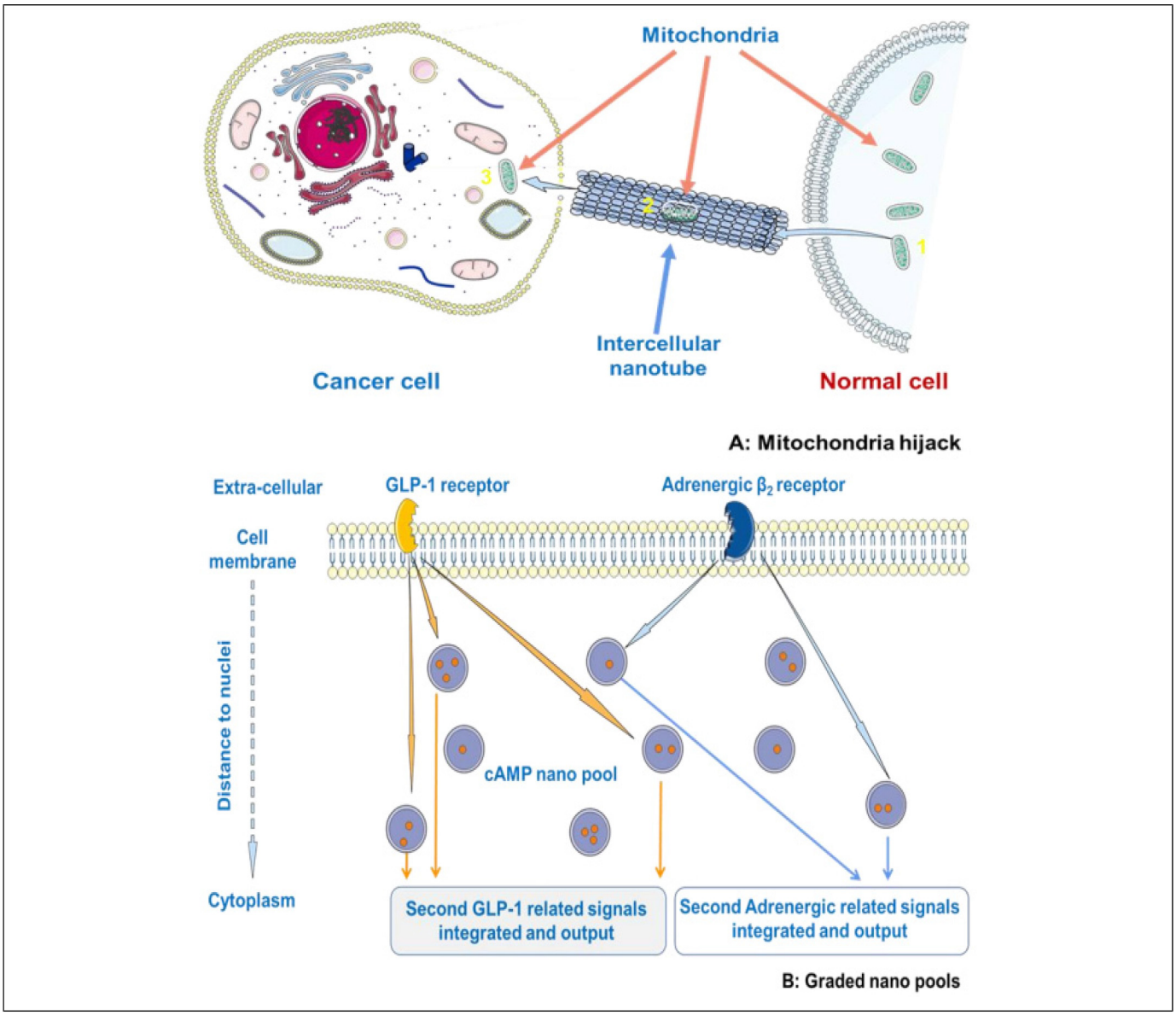

Figure 2. Schematic of biological nano confinements elucidated by mitochondria hijack (A) and graded messengers pools (B). These are two different types of BNCs both in structures and functions. The former is an innate structure-dominated BNCs undergoing the materials transportation between two different cells, and the latter is a functional body to perform the signaling transduction regulation. BNC, biological nano confinement.

recent study suggested that special nano-scale compartments possess a variable concentration of cAMP available in different cytoplasmic layers.[13] Individual GPCRs signals can interact with these compartments and release cAMP to access the terminators, initiating the cell functions (Figure 2B). For example, highly localized cAMP pools around glucagon-like peptide 1 (GLP-1) and β2 adrenergic receptors, are produced due to low concentrations of GLP-1 and isoproterenol, respectively. A single cell can operate thousands of independent cellular signals simultaneously instead of merely an "on/off" switch thanks to the coexistence of many such compartments.[13]

Furthermore, besides the above innate biological nano confinements (iBNCs)[5,12–15] using different techniques and equipment, other imaging and exploration works[16,17] of the life activities of living cells are ongoing, especially targeted on the most important organelles, such as the Golgi apparatus, which will facilitate to find much more types of BNCs in the future.

Based on the above findings and information, we propose a novel conception of iBNCs, which include any innate structural and functional nanodomains both extracellular and intracellular with spatial heterogeneity.

Conclusion

In summary, innate nanodomains widely exist in biological systems, which comprehensively impact cell fate and function. They possess superior bioaffinity compared to exogenous nanomaterials, are target specific, and controllable in nature. Cancer cells can proliferate and metastasize under essential and sufficient energy and materials supply, and adaptive signal transduction. These essential conditions may be regulated by various innate cellular nanodomains. With positive regulation, cancer cells can seize much more energy and materials for anabolism, then proliferate and metastasize, otherwise, they will shrink and die under the negative regulation. The characteristics of innate cellular nanodomains will facilitate the next generation of cancer therapeutics by regulating energy and anabolism. The new findings of cellular innate nanodomain may evoke a significant impact and shift the focus from exogenous nanomaterials to cellular innate nanodomains. This is an exciting time to be involved in harnessing the full potential of cellular innate nanodomains to advance cancer therapeutics.

Author Contributions

Jianshe Yang proposed the concept and designed the article; Zunqiang Zhao, Shu Deng, Zhongwei Lv, and Jianshe Yang analyzed and interpreted data for the article; Zunqiang Zhao and Jianshe Yang drafted the article and revised it critically for important intellectual content; All the authors approved the version to be published and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of Conflicting Interests

The authors declare no potential conflict of interest.

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