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New Technologies and Devices for Cancer Diagnosis

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Abstract:

For almost all cancers, the chances of survival are significantly increased if the disease is detected, diagnosed and treated at an early stage. This has triggered scientists to innovate methods for early cancer diagnosis and cancer cell analysis. Detection of exosomes, an important mediator of intracellular communication in cancer cells, is difficult because of several factors. These include expensive equipment, low sensitivity, and complicated procedures. Cell sieving based on tumor cell size is simple and effective, but there is a "fluid dead space" between the pores in the filtration process, which is prone to clogging and inconsistent cell filtration. In this paper, we introduce the latest tumor cell screening and collection tools. These new techniques are valuable for early diagnosis of cancer, guidance of surgical staging, and prognosis of surgery.

Key Words:
Cancer cell, cancer diagnosis, tumor cell screening

1.Introduction:

According to the "Global Cancer Report 2014" published by the World Health Organization (WHO) in 2017, the number of new cancer cases and deaths is increasing worldwide. 14 million new cancer cases and 8.2 million deaths were reported worldwide in 2012. According to the report "Cancer Statistics 2017" published online in CA: A Cancer Journal for Clinicians in 2017, men are most likely to develop prostate cancer, followed by lung (bronchial) and colorectal cancers. Women are most likely to develop breast cancer, followed by lung (bronchial) and colorectal cancers. The essential elements of cancer treatment are early detection, early diagnosis, and then early treatment.

Early-stage cancers are mostly confined to one organ, small in size, and do not infiltrate or slightly infiltrate the surrounding tissues and blood and lymphatic circulatory systems, and have a 5-year survival rate of 80% after surgery and other treatments, which greatly reduces the mortality rate of cancer. Due to the limitations of current diagnostic conditions and the lack of obvious signs in the early stage of cancer, the development of efficient, rapid and targeted cancer detection methods is of great significance for the diagnosis, treatment and prognosis of cancer.

Currently, there are many methods for cancer detection, such as x-ray [1], magnetic resonance imaging [2], and fluorescence imaging [3]. Although these techniques are effective and widely used, they require expensive instruments, long sample preparation and testing time, and highly specialized personnel. In addition, X-rays have the potential to induce malignancy due to their ionizable nature. Nuclear magnetic equipment is complex and expensive. Therefore, there is an urgent need for a detection method with non-ionizing and high sensitivity to help physicians identify cancer intraoperatively.

To overcome the existing limitations, biosensors for detecting cancer markers have the potential to replace the existing conventional cancer detection methods. Cancer markers may be molecules produced by tumor cells or specific responses or behaviors of the body's defense system in response to the presence of cancer. These biomarkers can include a wide range of biochemicals. Along with the development of terahertz technology, terahertz imaging can be used to detect cancer safely, efficiently, and with high sensitivity. In this paper, we explore the current novel cancer detection tools and future directions from both biosensors and terahertz imaging technology.

2. Discussion：

2.1 Tumor Cell Isolation Technology

The rare tumor cells latent in the pleural effusion of lung cancer patients may carry a wealth of tumor information. Obtaining and analyzing this information is expected to be used to guide the clinical diagnosis of lung cancer and to develop drug treatment plans. However, due to the rarity of these cells, it is still challenging to enrich suspected tumor cells with high purity and activity from a 100 mL volume of pleural fluid with high throughput and high recovery rate. The existing tumor cell sieving method based on tumor cell size is simple and effective, but there is a "fluid dead space" between the pores in the filtration process, which is prone to clogging. Inspired by the daily hand-brewed coffee, Cheng et al.[4] proposes an ascending strategy to turn traditional 2D filtration, into 3D filtration, which better overcomes the above shortcomings. Based on this idea, a funnel-shaped 3D spiral channel integrated cell sieve device ("3D cell sieve") was designed and used for enrichment screening of rare tumor cells from pleural effusions. The 3D cytoscreen device is a three-layer cone-shaped composite structure consisting of a funnel-shaped scaffold, a flexible microporous membrane in the middle, and a 3D spiral microfluidic channel snapped onto the membrane, as shown in Figure 1. It features a 3D spiral channel on the membrane to guide the spiral flow of the liquid sample containing rare cells on the membrane, so that small cells (background cells) and liquid are continuously filtered out during the flow, while large cells (target cells) eventually flow to the cone tip for final recovery, achieving high purity enrichment.

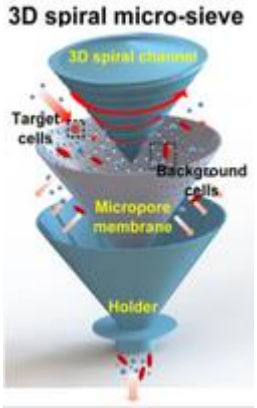

Fig.1 3D cell sieve [4].

The experimental results revealed that the following performance indicators could be achieved by simply pouring the sample to be analyzed into this 3D cell sieve without centrifugation or pressure drive: (1) throughput: the filtration throughput of up to 20 mL/min for triple dilution of whole blood samples, which is 20 times higher than that of the 2D method; (2) recovery: 100, 1000, 10000 in 30 mL PBS cells/mL could reach (84.5±21)%, (86±25)%, and (83±14)%, respectively, while the positive detection rate in samples with only 5 A549 cells in 1 mL PBS could all reach 100%; (3) in terms of purity: typically (85.5±9.1)% was achieved; and (4) in terms of cell activity: greater than 93%. Further, in the clinical sample experiments of this 3D cell sieve, the ability to rapidly and efficiently enrich rare tumor cells from 25 mL of clinical pleural fluid was achieved. Moreover, during the subsequent 6 days of culture of the enriched cell samples, it was found that the proliferation capacity of the enriched purified cells exceeded that of the unenriched cells by approximately 4.6-fold. The research results are expected to be developed into a practical tool to assist clinical tumor diagnosis and precision medicine in the future.

2.2 Exosome testing

Exosomes are mediators of intercellular communication and play an irreplaceable regulatory role in a number of key

biological processes. Since cancer cells release more exosomes than normal cells, some cancer-related biomarkers are overexpressed in cancer cells, and this information can reflect genetic or signaling alterations in cancer cells. Therefore, exosomes play an important role in the early detection and prognosis of cancer. It is increasingly recognized that exosomes hold promise as circulating biomarkers for various diseases. Research on the development of sensitive and rapid exosome assays has attracted extensive attention.

The development of the semiconductor industry has made field-effect transistors (FETs) the most essential electronic components in modern microelectronic integrated circuits (ICs) chips. In addition, their fast electrical response, high sensitivity and label-free detection offer great scope for biomolecular detection [5]. By chemically or biologically modifying the detection region, FET microelectronic devices form "biofield effect tubes" that are capable of electrically detecting various biomolecules with high sensitivity [6]. In a biofield effect tube, the interactions between biomolecules are converted into electrical reactions. The biosensor can output an electrical signal that is directly relayed by a subsequent information system. In addition, biofield effect tubes enable label-free and real-time detection. Biofield effect tubes can be fabricated using advanced complementary meta-oxide semiconductor fabrication techniques, and it is evident that biosensors have the potential to be mass-produced using manufacturing foundries.

Although, Si-NW-based biofield-effect transistors show great potential for ultrasensitive biomolecular detection [7] and have demonstrated the ability to detect proteins [8-10], nucleic acids [11], etc. However, there are still many unknowns about the newly discovered exosome biomarkers [10-13] compared to biomolecules as well as protein and nucleic acid analysis, for example, whether it is possible to detect relatively complex exosomes with Si-NW Bio-FETs. Therefore, Zhao et al [14] proposed a Si-NW biofield effector and demonstrated its application in their study for the detection of exosomes of tumor cell origin. the Si-NW biofield effector was successfully used for electrical and label-free exosome detection. It was shown that the Si-NW biofield effector can be used for accurate quantification of exosomes and real-time detection of antibody-exosome interactions. In addition, this Si-NW biofield effector has great potential for label-free and real-time biomarker detection in early disease diagnosis.

This study developed a highly sensitive Si-NW biofield effector for label-free detection of exosomes. In addition, Si-NW allows real-time monitoring of exosomes as the real-time current decreases with increasing exosome concentration. This study provides a new CMOS method for exosome detection, which is expected to be used for real-time monitoring and clinical diagnosis in the future.

2.3 Terahertz imaging techniques:

Terahertz (THz) waves are electromagnetic waves with frequencies from 0. 1 to 10 THz, located between infrared and microwave, which have properties such as non-ionization, fingerprint spectrum, and sensitivity to polar substances. Terahertz wave imaging has been widely studied in recent years as one of the candidate technologies for medical imaging. Terahertz wave imaging has been applied to the detection and identification of numerous tumor lesions [15-18], such as skin cancer, liver cancer, oral cancer, and brain glioma. Compared with normal tissues, tumor tissues have higher water content [19] and tumor cells have increased density, nuclear heterogeneity, mitotic activity, and necrosis [20], which will alter their refractive index, absorption, and scattering properties for detection in the THz band. (Usually, tissue water content is the ratio of the mass of water contained in the tissue to the wet weight of the tissue, and cell density is the ratio of the total number of cells to the volume of the tissue after digestion by enzymes.) Considering that the absorption coefficient of terahertz waves by water in fresh biological tissues is much larger than that of terahertz waves by other substances in the tissues, and that the water content in biological tissues is usually high, studies of fresh tissues in

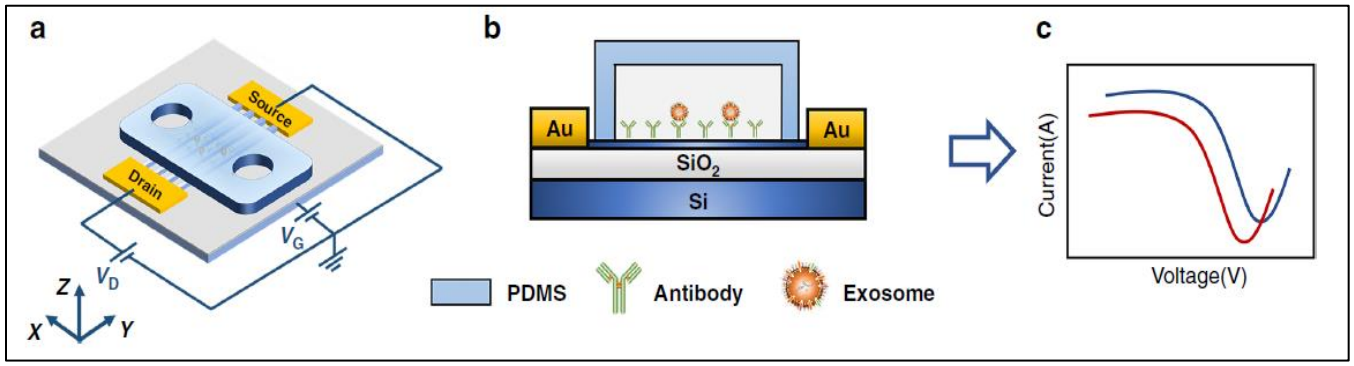

Fig. 2 a Schematic diagram of the Si-NW Bio-FET. b Schematic diagram of the Si-NW Bio-FET cross-section. c Schematic diagram of signal changes [14].

the existing literature have shown that the difference in water content is the main reason for the difference in THz spectra between tumors and normal tissues and studies of frozen and paraffin-embedded tissues have shown that differences in cell composition and morphology are also THz spectral properties between tumor and normal tissues. In 2016, S. Yamagu-chi et al. measured the spectral properties of fresh and paraffin-embedded rat glioma and normal tissues based on terahertz time-domain spectroscopy system (THz-TDS), and calculated by quantitative analysis that the water content in fresh glioma tissues was increased by approximately 5% compared to normal tissues, and the nucleus density per unit area of glioma tissues was higher than that of normal tissues. The nucleus density per unit area of glioma tissue is increased by more than 15% compared to normal tissue [21]. The combined effect of these two results in a higher refractive index in the tumor region than in the normal tissue.

In the detection of breast cancer tissue, the water content of cancer tissue is about 60%, while the water content of normal breast tissue is about 40% [22]. THz spectroscopy and imaging techniques have also been used to try to reveal differences in the characteristics of breast cancer and normal tissue. 2007, P. C. Ash-worth et al. reported that the refractive index and absorption coefficient of fresh ex vivo human breast cancer tissue in the range of 0. 15-2. 5 THz were higher than those of normal fat and fibrous tissue [23]. T. Bowman et al. reported that the refractive index and absorption coefficient of paraffin-embedded breast cancer samples were higher than those of normal adipose and fibrous tissues in the range of 0. 1-1. 2 THz [24]. In 2012, A. M. Hassan et al. used a reflective terahertz imaging system with frequencies of 2 THz and 3 THz to achieve tumor margin assessment of paraffin-embedded breast cancer samples [25]. in 2016, T. Bowman et al. used reflective and transmissive imaging systems with THz-TDS to achieve the differentiation of fresh ex vivo breast cancer tissue from fat and fibrous tissue, respectively, and demonstrated that reflective imaging has higher resolution and sensitivity in studying tumor region identification [26]. In addition, the team used the THz-TDS reflectance imaging system to perform three-dimensional imaging of three material simulants of breast invasive ductal carcinoma tissue, breast fibro glandular tissue, and fat, and experimentally placed the first two materials on the fat simulant, and the average reflection thickness could be measured as 392 μm based on the secondary reflection of the pulse, which is close to the actual thickness of 400 μm of fat [27]. Based on the previous research, we can expect that terahertz, as a new technological tool, will play a role in the field of cancer detection in the future.

3.Conclusion：

Currently, the incidence of cancer is increasing year by year. As cancer cells spread and form tumors in different organs, the mortality rate at the metastatic stage of cancer increases, so early cancer diagnosis is extremely important to improve the success rate of treatment. In the future, efficient, accurate and convenient cancer diagnosis and treatment tools will be a hot spot for research, and further research by researchers is needed.

References

[1] Feig S A，Hendrick R E. Radiation risk from screening mammography of women aged 40-49 years［J. Journal of the National Cancer Institute Monographs，1997，22（22）：119-124.
[2] Ravoori, M. K., Singh, S., Yang, P., Wei, W., Chen, H., Ma, J., ... & Kundra, V. (2020). In vivo magnetic resonance imaging of orthotopic prostate cancer. Biotechniques, 69(1), 37-45.
[3] Kang, C. C., Chang, C. C., Chang, T. C., Liao, L. J., Lou, P. J., Xie, W., & Yeung, E. S. (2007). A handheld device for potential point-of-care screening of cancer. Analyst, 132(8), 745-749.
[4] Cheng J, Zhang L, Zhang Y, Ye Y, Zhao W, Zhang L, Huang C, (2022). 3D spiral channels combined with flexible micro-sieve for high-throughput rare tumor cell enrichment and assay from clinical pleural effusion samples. Bio-Design and Manufacturing, 5(2), 358-370.
[5] Shen, M. Y., Li, B. R. & Li, Y. K. Silicon nanowire field-effect-transistor based biosensors: From sensitive to ultra-sensitive. Biosens. Bioelectron. 60, 101–111 (2014).
[6] Sung, D. & Koo, J. A review of BioFET’s basic principles and materials for biomedical applications. Biomed. Eng. Lett. 11, 1–12 (2021).
[7] Wu, C. C. et al. Label-free biosensing of a gene mutation using a silicon nanowire field-effect transistor. Biosens. Bioelectron. 25, 820–825 (2009).
[8] Zhang, N. et al. O2 plasma treated biosensor for enhancing detection sensitivity of sulfadiazine in a high-κ HfO2 coated silicon nanowire array. Sens.Actuators B: Chem. 306, 127464 (2020).
[9] Huang, Y. W. et al. Real-time and label-free detection of the prostate-specific antigen in human serum by a polycrystalline silicon nanowire field-effect transistor biosensor. Anal. Chem. 85, 7912–7918 (2013).
[10] Ma, J. et al. Rapid and sensitive detection of mycobacterium tuberculosis by an enhanced nanobiosensor. ACS Sens. 6, 3367–3376 (2021).
[11] Vu, C. A., Lai, H. Y., Chang, C. Y., Chan, H. W. & Chen, W. Y. Optimizing surface modification of silicon nanowire field-effect transistors by polyethylene glycol for MicroRNA detection. Colloids Surf. B. Biointerfaces 209, 112142 (2021).
[12] Malsagova, K. A. et al. Highly sensitive detection of CA 125 protein with the use of an n-type nanowire biosensor. Biosensors https://doi.org/10.3390/bios10120210 (2020).
[13] Su, P. C., Chen, B. H., Lee, Y. C. & Yang, Y. S. Silicon nanowire field-effect transistor as biosensing platforms for post-translational modification. Biosensors https://doi.org/10.3390/bios10120213 (2020).
[14] Zhao W, Hu J, Liu J, Li X, Sun S, Luan X, Zhao Y, Wei S, Li M, Zhang Q, Huang C. Si nanowire Bio-FET for electrical and label-free detection of cancer cell-derived exosomes. Microsyst Nanoeng. 2022 May 30;8:57.
[15] Joseph C S，Patel R，Neel V A，et al. Imaging of ex vivo nonmelanoma skin cancers in the optical and terahertz spectral regions optical and terahertz skin cancers imaging［J］. Journal of Biophotonics，2014，7(5):295-303.
[16] Grootendorst M R，Fitzgerald A J，Koning S G，et al. Use of a handheld terahertz pulsed imaging device to differentiate benign and malignant breast tissue［J］. Biomedical Optics Express，2017，8(6): 2932-2945.
[17] Ji Y B，Oh S J，Kang S G，et al. Terahertz reflectometry imaging for low and high grade gliomas［J］. Scientific Reports 6，2016：36040.

[18] Sim Y C，Park J Y，Ahn K M，et al. Terahertz imaging of excised oral cancer at frozen temperature［J］. Biomedical Optics Express，2013, 4(8): 1413-1421.
[19] Png M G，Choi W J，Ng H W B，et al. The impact of hydration changes in fresh bio-tissue on THz spectroscopic measurements［J］. Physics in Medicine and Biology，2008，53(13):3501-3517.
[20] Wesseling P，Kros M J，Jeuken J. The pathological diagnosis of diffuse gliomas：towards a smart synthesis of microscopic and molecular information in a multidisciplinary context［J］. Diagnostic Histopathology, 2011, 17(11):486-494.
[21] Yamaguchi S, Fukushi Y, Kubota O, et al. Origin and quantification of differences between normal and tumor tissues observed by terahertz spectroscopy［J］. Physics in Medicine & Biology, 2016, 61(18):6808-6820.
[22] G. Bindu，S. J. Abraham，A. Lonappan，et al. Detection of dielectric contrast of breast tissues using confocal microwave technique［J］. Microwave and Optical Technology Letters, 2006, 48(6)：1187-1190.
[23] Ashworth P C，Pickwell-MacPherson E，Pinder S E，et al. Terahertz Spectroscopy of Breast Tumors［C］. International Conference on Joint International Conference on Infrared & Millimeter Waves,2007.
[24] Bowman T，Shenaweea M E，Campbellb L. Regional spectroscopy of paraffin-embedded breast cancer tissue using pulsed terahertz transmission imaging［C］. Conference on Optical Interactions with Tissue and Cells XXVII，2016.
[25] Hassan A M，Hufnagle D C，Shenawee M E，et al. Terahertz imaging for margin assessment of breast cancer tumors［C］. International Microwave Symposium Digest IEEE Mtt S International Microwave Symposium，2012.
[26] Bowman T，Shenawee M E，Campbell L K. Terahertz transmission vs reflection imaging and model-based characterization for excised breast carcinomas［J］. Biomedical Optics Express,2016,7(9): 375-3783.
[27] Bowman T，Walter A，El-Shenawee M. Margin assessment of three-dimensional breast cancer phantoms using terahertz imaging［C］. Conference on Design and Quality for Biomedical Technologies IX，2016.

