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Chemical Nose Sensors – an Alternative Strategy for Cancer Diagnosis

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Introduction

Cancer diagnoses come in two forms: 1) Does the patient have cancer? 2) What kind of cancer (i.e. phenotype) is present? Both questions are important, however the answer to the second question is what dictates the course of therapy to be used. Conventional cancer detection methods rely on “lock and key” specific recognition of specific biomarkers to provide diagnostic information. This biomarker-based approach is complicated by the highly variable and plastic nature of tumors. For example, prostate-specific antigen is an important marker for prostate cancer; unfortunately, its concentration level is similar in both benign and malignant tumors [1]. Very often, one or two biomarkers are not adequate to detect different cancer types [2,3], making choice of therapy a hit-or-miss affair.

Profiling the overall physico-chemical changes in tumor cells provides an alternative strategy to cancer diagnostics. One approach is to use “chemical nose” array sensors, where selective interactions between the sensors and analytes generate distinct patterns [4], analogous to our own sense of smell. Just like with our own noses, chemical nose sensors do not require a previous knowledge of the analytes and are instead “trained” to recognize analytes [5,6]. Array-based sensors have been used widely in detecting different chemicals ranging from volatile organic compounds, amino acids, proteins, and carbohydrates [7,8,9,10]. More recently, this approach has been extended to more complex systems, including bacterial [11] and mammalian cell surfaces [12,13,14,15]. We recently developed an unbiased gold nanoparticle-based array sensor to detect cancer cells as well as complex tumor tissues [16]. Until this year, however, this approach has not been applied to actual tumor diagnosis, a much more complicated system.

Array-based sensor designs and principles

Biosensors have two functional components: recognition elements and transducers. Recognition elements are used to recognize and bind to the target analytes. Nanomaterials,

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specifically, gold nanoparticles (AuNPs) provide a versatile scaffold for recognition elements, owing to their large surface area that facilitates multivalent interactions of the AuNPs with the analytes. AuNPs also possess the tunable surface functionalities required for selective binding, a prerequisite to “nose”-based strategies. Direct transduction of the binding of AuNPs is challenging, however, they feature strong quenching ability due to the gold core [17]. This photophysical property enables the use of fluorescent displacement assays, where displacement of a fluorophore from the recognition element signals the binding event [18]. We found excellent candidates as a transducer such as poly(p-phenyleneethynylene) (PPE) and green fluorescent protein (GFP) [12,13]. More recently, sensing systems have been designed using one species with a dual role of recognition element and transducer, such as magnetic glyco-nanoparticle (MGNP) arrays and nanomaterial-assisted chemiluminescence [14,15].

Cell surface sensing

Cell surface functionality including polysaccharides, proteins, and lipids vary depending upon cell types and states [19,20]. We generated a sensor for cell type and state based on these changes in cell surface fingerprints. In this initial study, we used three cationic AuNPs for an array of recognition elements and a negatively charged PPE polymer (PPE-CO₂) as the transducer. The AuNPs quenched the polymer due to complexation *via* electrostatic interactions. After incubation with cells, differential binding affinity between the cell surface and the cationic AuNPs causes different fluorescence restoration levels of PPE-CO₂, generating distinct fingerprint signals for each cell type. This cationic AuNPs–PPE-CO₂ sensor successfully differentiated between human breast cell lines, including cancerous (MCF-7), metastatic (MDAMB-231) and normal cell lines (MCF10A). However, these cell lines came from different individuals, with a possible effect of genetic variation. To avoid the issue of individual-to-individual variation, we used isogenic cell lines derived from BALB/c mice: CDBgeo (normal), TD (cancerous), and V14 (metastatic). Owing to the high genetic similarity, isogenic cell lines are excellent testbeds for our sensor validation. The sensor array readily detected the difference between these cells, demonstrating the utility of this method for cell surface sensing [12]. Later studies used green fluorescent protein (GFP) as a transducer, providing higher sensitivity, using 5,000 cells as compared to 20,000 cells used in the AuNP-polymer system [13].

In another approach, magnetic glyco-nanoparticles (MGNPs) were used for array-based sensing. In this system, MGNPs produced different degree of aggregation upon incubation with the cells, generating different local magnetic field gradients and altering the transverse relaxation time (T₂). The MGNPs array system based on magnetic resonance imaging (MRI) signatures differentiated several cancer cell types with a sensitivity of 10⁵ cells/mL [14]. Similarly, cancerous cells were detected using a reusable nanomaterial-assisted chemiluminescence array sensor. Thermochemiluminescence of different cell lines were studied on ceramic heaters sintered with catalytic nanomaterials, resulting in a variety of distinctive patterns [15]. Taken together, array-based sensors have been employed effectively in cancer cell detection based on subtle changes in extracellular signatures.

Tissue sensing

The heterogeneity of tissues makes real-world diagnosis of cancer much more challenging than the well-controlled conditions found with cultured cells. Tissues are inherently complex, containing diverse cell types such as epithelial, endothelial, muscle, and immune cells, as well as necrotic/apoptotic cell states. Moreover, the extracellular matrix of these materials is equally complex. Given this complexity, we focused our studies on tissue sensing using tissue lysates, focusing on differences in the proteome of diseased and healthy tissues. For our studies, we employed an *in vivo* metastasis model created by using NCI-H1299 non-small-cell lung cancer cells. Tissue homogenates were prepared from tissues samples (corresponding to fine needle biopsies commonly used for tumor histology) using lysis buffer that contained protease inhibitors. The protein content of the tissue lysates was quantified and kept constant. These lysate samples were sensed using an array of GFP-AuNP conjugates. This approach was quite effective: site-specific metastatic tissues were readily differentiated from each other as well as the corresponding healthy tissue, providing a potentially robust and efficient tool for clinical diagnostics [16].

Challenges in array-based sensing

One of the strengths of “nose”-based sensing is the versatility of the methodology. This versatility provides a challenge: array-based sensors need to be retrained and validated for each new analyte. The sensitivity of the system is likewise a blessing and a challenge, as baseline profiles for known samples must be carefully examined to maximize accuracy [19]. Perhaps the greatest challenge of “nose”-type sensing is the fundamental difference between this method and other biomarker-based strategies. Just like our sense of smell, sensing using olfaction mimics is inherently hypothesis-free, a situation many researchers are not yet comfortable with.

Conclusions

Chemical nose sensors present an alternative pathway in biosensing, complementing the capabilities of specific biomarker-based approaches. For clinical application, array-based sensors can provide a robust and generic tool for detecting and identifying cancer. Notably, this unbiased array-based strategy can be employed as a personalized screening device, where an individual's health is monitored at different time points. By tracing the map of known profiles, the array-based sensor is capable of decoding one's health stages and revealing alarm signals aiding disease prognostication and diagnosis.

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Biographies

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