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Key words: cancer detection, cell sensing, nanoparticles, sensor arrays, nanotechnology

Most biomolecular and cell surface sensing strategies use specific interactions between antibodies and target analytes, e.g., ELISA and antibody arrays. Sensory processes such as taste and smell, however, use differential binding where the receptors interact with their analytes by selective rather than specific binding events. Applying this approach to sensors, a.k.a. “chemical noses”, provides a potentially powerful alternative to traditional immunosensor methods. In the “nose” approach, an array of different receptors is generated, with the individual elements of the array responding to a range of different analytes.1 The distinct response pattern generated from the array then provides a fingerprint for classification and/or identification of the target.2

While nose-based sensing has been used extensively for small molecule detection, this approach has only recently been applied to biomacromolecules, including proteins.3 In general, these studies have focused on identification of specific analytes. One can apply these sensors in a very different way, however. Using the analogy of the human nose, we can not only identify specific odors, but we can also tell by subtle and rather complex changes in smell if something is “off”, e.g., spoiled meat or vegetables. Extending this to nose-based sensors, it is logical that subtle changes in cell surface properties and functionalities might be used to sense and identify cell types, as well as differentiate between healthy and cancerous cells. Proof of principle for this strategy was provided by studies where we were able to differentiate between bacterial species and even between different strains of the same species using nanoparticle-polymer sensors.4

Our demonstration of the use of nose-based sensing of mammalian cells began with differentiating between cell types using a simple sensor array comprised of three nanoparticles and one polymer (Fig. 1A).5 In this system, electrostatic attachment of the fluorescent polymer to the particle quenches polymer fluorescence. Binding of the particle to cell surfaces displaces the polymer, providing the response used for sensing (Fig. 1B). We chose four cell lines for our initial studies: liver (HepG2), cervix (HeLa), testis (NT2) and breast (MCF-7). Each of these cell types has functions that would generate cell surface differences, hence our expectation was that these cell lines would be readily differentiated. In our studies, we were able to readily differentiate between suspensions of each of these cell lines. Differentiating between healthy, cancerous and metastatic cells would be expected to be more difficult than sensing cell types. Our next studies focused on human breast cell lines, where we were able to differentiate between normal (MCF10A), cancerous (MCF-7) and metastatic (MDA-MB-231) cell lines.

While the studies with human cancer cells were promising, there was one key question that we could not answer: were we differentiating between cell states or between the different subjects the cells were obtained from? To eliminate interference arising from individual differences, we used three isogenic cell lines derived from BALB/c mice. The identical genetic origin of these cells makes them an excellent model for cancer detection in a biomedical context. For our studies, we utilized CDBgeo (normal)6 TD (cancerous) and V14 (invasive)7 cell lines. As with our prior studies, each of these cell lines could be rapidly and reproducibly differentiated (Fig. 1C).

Overall, the results of this study are promising. Differentiation between healthy, cancerous and metastatic cells was achieved in a matter of minutes using a standard plate reader. Moreover, only three different nanoparticles were required to achieve this differentiation, suggesting that a large number of cell types/states could be differentiated by increase the number of sensor elements in the array. As such, the methodology has immediate potential in terms of cell screening for carcinogenicity and other in vitro applications. Application of this method to cancer diagnostics is far more challenging, as issues of tissue heterogeneity will need to be addressed, an effort we are currently undertaking.

Support from the NSF (DMI-0531171) and NIH (GM077173 and AI073425) is gratefully acknowledged.

References
Figure 1. Molecular structures of nanoparticles and polymers, and schematic of fluorophore displacement cell detection array. (A) Molecular structures of the cationic gold nanoparticles (NP1-NP3) and the fluorescent polymer (PPECO2); (B) Displacement of quenched fluorescent polymer (dark strips, fluorescence off; light strips, fluorescence on) by cell with concomitant restoration of fluorescence. (C) Detection of isogenic cell types: change in fluorescence intensities (F-F0) for three cell lines of same genotype CDBgeo, TD cell and V14 using nanoparticle-polymer supramolecular complexes. Each value is the average of six parallel measurements.