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Redox-labeled Electrochemical Aptasensor Array for Single-cell Detection

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Abstract : The need for single cell detection and analysis techniques has increased in the past decades because of the heterogeneity of individual living cells, which increases the complexity of the pathogenesis of malignant tumors. In the search for early cancer detection, high-precision medicine and therapy, the technologies most used today for sensitive detection of target analytes and monitoring the variation of these species are mainly including two types. One is based on the identification of molecular differences at the single-cell level, such as flow cytometry, fluorescence-activated cell sorting, next generation proteomics, lipidomic studies, another is based on capturing or detecting single tumor cells from fresh or fixed primary tumors and metastatic tissues, and rare circulating tumors cells (CTCs) from blood or bone marrow, for example, dielectrophoresis technique, microfluidic based microposts chip, electrochemical (EC) approach. Compared to other methods, EC sensors have the merits of easy operation, high sensitivity, and portability. However, despite various demonstrations of low limits of detection (LOD), including aptamer sensors, arrayed EC sensors for detecting single-cell have not been demonstrated. In this work, a new technique based on 20-nm-thick nanopillars array to support cells and keep them at ideal recognition distance for redox-labeled aptamers grafted on the surface. The key advantages of this technology are not only to suppress the false positive signal arising from the pressure exerted by all (including non-target) cells pushing on the aptamers by downward force but also to stabilize the aptamer at the ideal hairpin configuration thanks to a confinement effect. With the first implementation of this technique, a LOD of 13 cells (with5.4 µL of cell suspension) was estimated. In further, the nanosupported cell technology using redox-labeled aptasensors has been pushed forward and fully integrated into a single-cell electrochemical aptasensor array. To reach this goal, the LOD has been reduced by more than one order of magnitude by suppressing parasitic capacitive electrochemical signals by minimizing the sensor area and localizing the cells. Statistical analysis at the single-cell level is demonstrated for the recognition of cancer cells. The future of this technology is discussed, and the potential for scaling over millions of electrodes, thus pushing further integration at sub-cellular level, is highlighted. Despite several demonstrations of electrochemical devices with LOD of 1 cell/mL, the implementation of single-cell bioelectrochemical sensor arrays has remained elusive due to their challenging implementation at a large scale. Here, the introduced nanopillar array technology combined with redox-labeled aptamers targeting epithelial cell adhesion molecule (EpCAM) is perfectly suited for such implementation. Combining nanopillar arrays with microwells determined for single cell trapping directly on the sensor surface, single target cells are successfully detected and analyzed. This first implementation of a single-cell electrochemical aptasensor array based on Brownian-fluctuating redox species opens new opportunities for large-scale implementation and statistical analysis of early cancer diagnosis and cancer therapy in clinical settings.

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