Mid-Infrared Resonant Nanostructures for Ultrasensitive Detection and Molecular Characterization of Tumor-derived Extracellular Vesicles

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Extracellular Vesicles (EVs) possess great potential for cancer liquid biopsy and personalized medicine because of their abundance in biofluids and specific molecular content representing the originating cells. Despite this potential, the translational process of EVs in diagnostics is still hindered by several limitations, as their biochemical characterization might require extensive post-labeling processes, large sample amounts, and often gives information on a single antigen at a time. In this context, Fourier Transform Infrared (FTIR) spectroscopy in the mid-infrared (IR) range is rapidly emerging as a promising route to provide label-free biochemical information on EVs in terms of their entire lipid, protein, and nucleic acid content. Inconveniently, the low molecular absorption cross-section of mid-IR vibrations and strong water absorption pose difficulties in characterizing minute analyte quantities in a liquid environment, which is desirable for EV-based diagnostic applications. Here, we present mid-infrared plasmonic nanoantenna arrays specifically designed for the detection of EVs' vibrational absorption signal in both liquid and dry phases, along with the unspecific refractive index sensing signal. To achieve this, EVs are immobilized on a gold nanoantenna surface using immunocapture, enabling the selection of specific EV sub-populations and removal of contaminants. Our device has undergone testing through in vitro experiments, employing an epithelial-mesenchymal transition model on intestinal cells, as well as utilizing vesicles derived from oncology patients with hepatocellular carcinoma and colorectal cancer. The high protein sensitivity and the ability to work with small sample volumes—two crucial attributes for ultrasensitive EV detection—demonstrate that our platform can contribute to the development of novel laboratory medicine techniques for the molecular characterization of EVs.