Virus Infection-on-a-Chip: A Bioelectronic Platform to Examine Virus Entry

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Viral infection begins when a virus particle breeches the host plasma membrane and successfully delivers its genome into that cell. Though these processes must occur for every viral pathogen that infects a host cell, the entry route can vary depending on the viral pathogen, the host cell type, and the local microenvironmental conditions. Virus particles are responsive to their environment and use cues from it to adapt and successfully time the entry process into the host cell. It is a continual evolutionary battle between the host and the virus to thwart infection and disease. For example, in SARS Coronavirus-2 (SARS-CoV-2), viral mutation rates frequently outpace the development of technologies used to detect and identify emerging variants of concern (VOC). Given the continual emergence of VOC, there is a critical need to develop platforms that can identify the presence of a virus and readily identify its propensity for infection. We built an electronic biomembrane sensing platform that recreates the multifaceted and sequential biological cues that give rise to distinct SARS-CoV-2 virus host cell entry pathways and reports the progression of entry steps of these pathways as electrical signals. Within these electrical signals, two necessary entry processes mediated by the viral Spike protein, virus binding and membrane fusion, can be distinguished. Our device has no living cells and our assay design faithfully replicates the biological cues governing virus response and the selection of distinct entry pathways, mirroring natural occurrences. We can swiftly (in tens of minutes) assess and differentiate the functional traits of VOC. Using this approach, we studied SARS-CoV-2 VOC (Wuhan-Hu-1, Omicron BA.1, and BA.4). We find that these closely related VOC exhibit distinct fusion signatures that correlate with trends reported in cell-based infectivity assays, allowing us to report quantitative differences in fusion characteristics among them that inform their infectivity potentials. This achievement, to our knowledge, marks the first application of a cell-free, virus-free, and label-free system for this purpose.