A virus-free impedance platform to emulate virus-induced cell fusion

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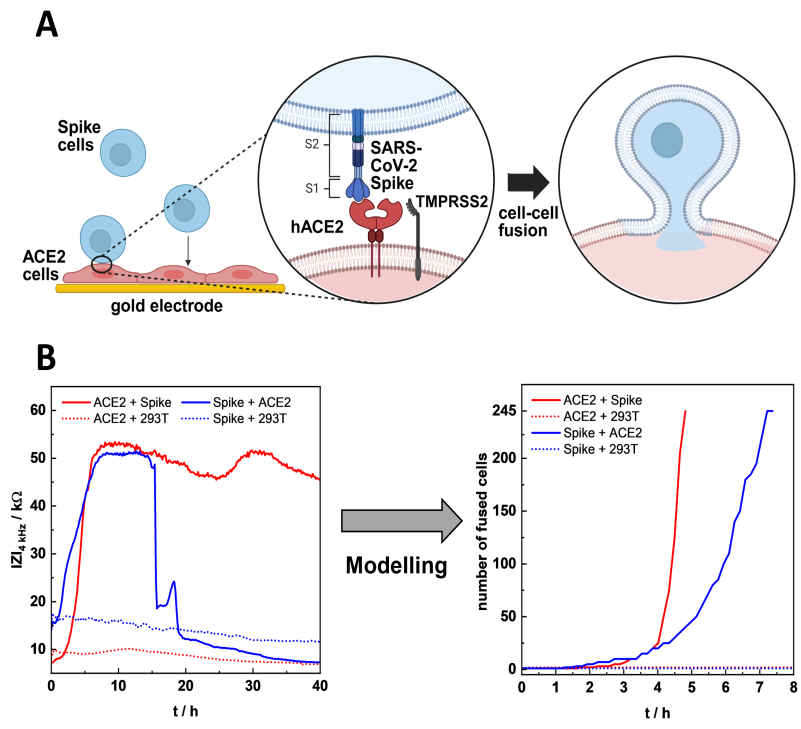
Monitoring cell fusion is essential for understanding viral infections and the development of antiviral therapies [1]. While fusion is typically observed by detecting morphological changes or exchange of intracellular materials microscopically [2], this study used impedance spectroscopy to assess cell fusion between two types of HEK293 cells: (i) HEK cells expressing the ACE2 receptor and (ii) HEK expressing the SARS-CoV-2 spike protein upon doxycycline induction. The latter serves as model for SARS-CoV-2 virus. In this project, impedance was monitored focusing on changes associated with cell-cell fusion. We found out that a time-dependent impedance increase at 4 kHz correlates with the extent of cell fusion between HEK-ACE2 and HEK-Spike, therefore, impedance magnitude can be used as a reliable measurand for evaluating cell fusion. In a second approach, we seeded HEK-ACE2 and HEK-Spike cells as co-cultures on electrodes and were able to induce cell-cell fusion at any selected time points by the addition of doxycycline, which served as inducer molecule for the expression of the spike protein in HEK spike cells in our system. Moreover, the intro-duction of anti-SARS-CoV-2 antibodies to the cell mixtures reduced the impedance increase, indicating inhibition of fusion through neutralization of the spike protein. A three-parameter fit model was applied to predict the number of fused cells without the need for staining or microscopy. Our results indicate that cell fusion is completed within 10 hours and involves almost all cells on the electrode. This approach provides a new impedance-based assay for detecting cell fusion in general, fusion as a consequence of viral infection and also to screen and to evaluate neutralizing antibodies with the capacity for high-throughput campaigns.



Impedance-based monitoring of receptor-mediated cell-cell fu-sion. **(A)** Schematic of experi-mental setup: cells expressing ACE2 cells are cultured on gold-film ECIS electrodes. Impedance is continuously measured during the addition of HEK cells ex-pressing the SARS-CoV-2 spike protein (or vice versa). Upon contact between the two cell types, membrane fusion – mi-micking the natural viral entry mechanism – is initiated. **(B)** Left: impedance time courses of cell-cell fusion (solid curves) and con-trol conditions (dashed curves). Right: prediction of number of fused cells after 3-parameter modelling. The model only allows for syncytia of ≤245 cells, bigger cell clusters are not predictable yet.

References:

[1] J.M. White and G.R. Whittaker, *Traffic* 17 (2016) 593-614.
[2] S. Martens and H.T. McMahon, *Nat Rev Mol Cell Biol* 9 (2008) 543-556.