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Genomics of Vero cells: Understanding this cell line and its virus-host interactions for improved vaccine production

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GENOMICS OF VERO CELLS: UNDERSTANDING THIS CELL LINE AND ITS VIRUS-HOST INTERACTIONS FOR IMPROVED VACCINE PRODUCTION

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The Vero cell line is the most used continuous cell line for viral vaccine manufacturing with more than 40 years of accumulated experience in the vaccine industry. Additionally, the Vero cell line has shown high affinity for infection by MERS-CoV, SARS-CoV and recently SARS-CoV-2, emerging as an important discovery and screening tool to support the global research and development efforts in this COVID-19 pandemic. Furthermore, Vero cells anchorage-dependent use renders scaling-up challenging and operations very labor intensive which affects cost effectiveness. Thus, efforts to adapt Vero cells to suspension cultures have been invested but hurdles such as the long doubling time and low cell viability remain to be addressed.
However, the lack of a reference genome for the Vero cell line has limited our understanding of host-virus interactions underlying such affinity of the Vero cell towards key emerging pathogens, and more importantly our ability to re-design high-yield vaccine production processes using Vero genome editing. In this study, we present an annotated highly contiguous 2.9 Gb assembly of the Vero cell genome. In addition, several viral genome insertions, including Adeno-associated virus serotypes 3, 4, 7 and 8, have been identified, giving valuable insights into quality control considerations for cell-based vaccine production systems. Variant calling revealed that, in addition to interferon, chemokines and caspases related genes lost their functions. Surprisingly, the ACE2 gene, which was previously identified as the host cell entry receptor for SARS-CoV and SARS-CoV-2, also lost function in the Vero genome due to structural variations.
In addition, a functional genomics analysis of the Vero cells adapted to suspension is performed to better understand the genetic and phenotypic switches at play during the adaptation of Vero cells from anchorage-dependent to suspension cultures. Results show a downregulation of the epithelial to mesenchymal transition (EMT) pathway, highlighting the dissociation between the adaptation to suspension process and EMT. Surprisingly, an upregulation of cell adhesion components is observed, notably the CDH18 gene, the cytoskeleton pathway, and the extracellular pathway. Moreover, a downregulation of the glycolytic pathway is balanced by an upregulation of the asparagine metabolism pathway, promoting cell adaptation to nutrient deprivation. A downregulation of the adherens junctions and the folate pathways alongside with the FYN gene are possible explanations behind the currently observed low cell viability and long doubling time.

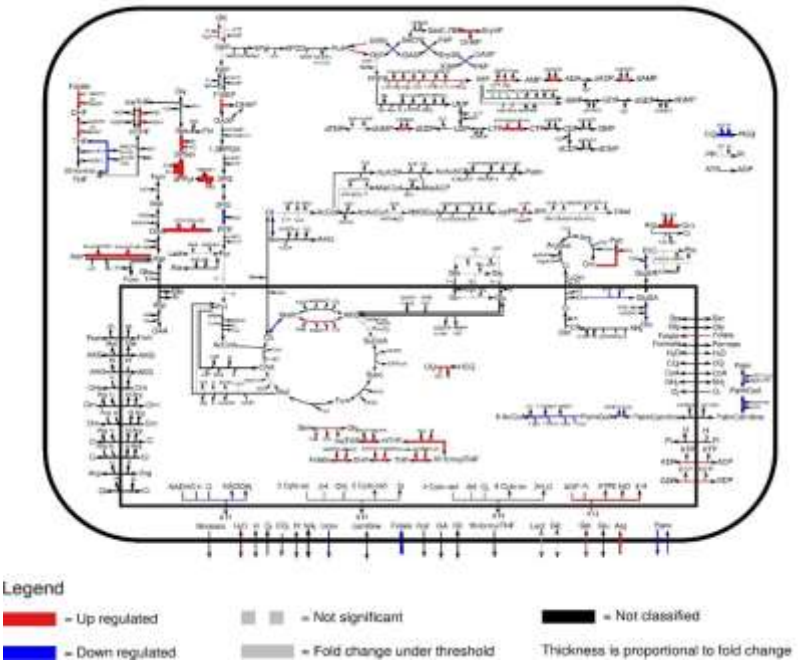

Figure 1 – Adherent and suspension Vero cell cultures comparative metabolic map. Blue and red arrows refer respectively to downregulated and upregulated reactions. Dashed gray arrows refer to non-significant dysregulations according to Kolmogorov-Smirnov test with p-value 0.01. Solid gray arrows refer to reactions with a variation lower than 20%