IMPLICATIONS OF MDCK CELL HETEROGENEITY IN CELL-BASED INFLUENZA VACCINE PRODUCTION

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Influenza is a global public health issue that causes serious illness with high mortality rate. Currently, Madin-Darby canine kidney (MDCK) cell culture-based influenza vaccine production moving up to the front as an inexorable trend for the substitution of egg-based vaccine production, owing to its high degree of flexibility and scalability. However, MDCK cells are a continuous cell line and comprise a heterogeneous pool of non-clonal cells that differ in morphological as well as functional features in influenza virus production. The impurity of cell population may lead to fugacious tendency in virus production, and long-term culture may bring potential risk of unstable viral production or vaccine quality as cells in MDCK subclonal population may encounter unexpected manifestation of chromosomal rearrangement, loss of the virus susceptibility, or reduction of the virus partials packaging capability during the culture. Although many details of the influenza virus life cycle have already been unraveled, little is known about the ability of subclones in virus infection, intracellular replication, and virus release during viral vaccine production process. With the widely utilizing of omics-based approaches and progressively accumulating of omics database, transcriptome profile analysis will be a powerful strategy to explore the mechanism of cell heterogeneity, providing great significance for the development of robust virus producing cell line and robust virus production process. This work aims to explore a deeper understanding on the MDCK cell heterogeneity used in influenza virus production. For this purpose, a MDCK cell line that has been extensively used in industrial production was subcloned and examined for the influenza virus productivity. The virus productivity spread over a wide range of more than 300-fold among different clones, which revealed large variations in their ability to produce progeny viruses. The high and low producer as well as parent cell population were expanded to explore the intracellular virus propagation process, and the expression levels of all the annotated genes were quantified across the different subclones using RNA-seq. The RT-qPCR results showed that the influenza virus RNA synthesis and virus release differed dramatically among subclones during a synchronized single-cycle infection. Pathway analysis performed on the genes indicated that most of the genes are not differentially expressed, but a few key cellular metabolic pathways are differentially expressed among the subclones, especially the genes related to the virus infection, replication and release. These results spurs further hypothesis to improve our mechanistic understanding of cell line stability and virus propagation process, which will have significant impact on rationalizing cell line development of viral vaccine producing mammalian cells.