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Short Commentary

Human iPSC-based Model of Coxsackie Virus B3: Groundbreaking new Approach for (Coxsackie-) Virus Research?

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COMMENTARY

Disease models are powerful tools to understand aspects of the underlying disease and to perform drug screening. A good disease model should be one that can closely mimic the actual pathology of the disease in patients and are practical for researchers to use and study. Especially in the current times of a virus pandemic, virus research is of highest importance.

In the recently published research article from Peischard et al. [1] a novel virus disease model was generated that could be beneficial for (Coxackie-) virus research. But how promising is the model? In their study, they were able to ectopically induce a non-infectious form of Coxsackie Virus B3 (CVB3ΔVP0) in human induced pluripotent stem cells (hiPSC) in a dose-dependent, time-dependent, and localized manner. The advantages (see Figure 1) of this system are: 1) It is a human model and not an animal model, in which effects can differ tremendously from human disease [2]. 2) There is a high availability of virus-expressing samples as hiPSCs can replicate virtually indefinitely in contrast to human patient biopsies. 3) Since it is an iPSC-based model, iPSC gene-editing can be performed or obtained from patients making it possible to analyze genetic effects on viral disease progression. 4) Viral effects can be analyzed *in-vitro* in potentially any kind of human cell type by differentiation of these human iPSCs. 5) The model system is non-infectious and can be handled in laboratories with low biosafety level in contrast to infecting cells with infectious particles [3]. 6) As virus induction can be dose- and time-dependently controlled, different infection scenarios such as acute, chronic, milder, or more severe infections due to lower or higher viral loads can be modeled. 7) Because it can be locally controlled, infection plaques can be modeled where the effect of the virus on neighboring healthy tissue can be analyzed.

Peischard et al. were able to verify the effectiveness of this model by showing effects of CVB3 on differentiated cardiomyocytes that correlated with previous observations in different models such as the elevated reactive oxygen species (ROS) level after CVB3 infection in mouse models mediated through Heme Oxygenase-1 [4,5], the disruption of intracellular cell membranes including the endoplasmic reticulum also seen in *in-vitro* transfection of CVB3's viroporin 2B in mammalian cells [6,7], and the fragmentation of mitochondria also seen in *in-vitro* transfection of recombinant and infectious CVB3 genome in mouse embryonic fibroblasts that has been claimed to be caused by CVB3 triggering Dynamin-related protein 1 (Drp1) [8].

However, despite these clear advantages there exist limitations or challenges (see Figure 1) as well: Since it is an *in-vitro* disease model, effects of the immune system cannot be studied in a monoculture. As the immune system has been shown before to have protective and adverse effects in viral inflammations, this would be an aspect of interest to understand the disease and find better treatment [9]. However, there may be little limitation to study intracellular immune responses against the virus like Jak-Stat or MAVS signaling. Although it is an advantage for laboratories with lower biosafety level to have a model that does not produce virus particles due to the introduced point mutations in the viral capsid, it is a disadvantage if effects of the virus particles i.e. viral docking and entry into the cell membrane and in the cell nucleus, are to be investigated. Moreover, intracellular effects of proteins of the viral capsids were also reported e.g. CVB3's VP1 inducing cell cycle arrest at G1 phase [10]. In those cases, Peischard et al.'s model can be modified to use the non-mutated wildtype genome of the virus, which would require laboratories that are equipped for handling organisms with higher biosafety level. In Peischard et al.'s study, they used CVB3 as the virus model, whereas the relatively small CVB3 genome of 7.4 kb provided a technical advantage. Evidently, there could be technical challenges to introduce other viruses with larger genomes such as SARS-CoV-2 with a genome size of 29.8 kb to 29.9 kb [11]. In addition, reprogramming cells to hiPSCs and *in-vitro* cell differentiation protocols from iPSCs to disease relevant cell types so far are still not perfect, not trivial to handle, and often create somewhat heterogeneous cell populations. However, constant optimizations of differentiation protocols and recent advances for more complex hiPSC-based systems are being made. These include three-dimensional organoids, tissue-engineering, microfluidic organ-chips, and humanized animal systems, which Peischard et al's model could potentially be applied to [12,13]. With Peischard et al.'s model it is possible to induce virus expression via supplementation of a tetracycline due to its Tet-On system. However, it would also be interesting if the removal of tetracycline after induction would lead to a cease in viral induction giving the possibility to study effects after recovery of an infection.

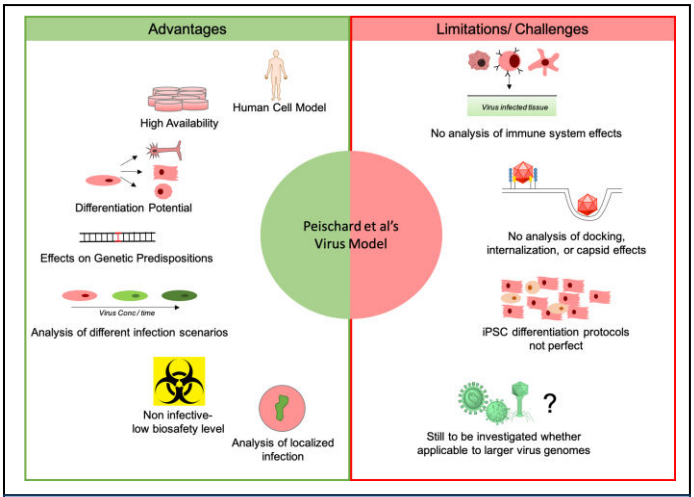

Figure 1: Advantages and limitations/ challenges of Peischard et al.'s virus model for (Coxsackie-) virus research.

CONCLUSION

In conclusion, Peischard et al.'s virus model represents a promising contribution to (Coxsackie-) virus research, as it could be used in most laboratories, be more easily accessible, non-infectious, and patient-specific. There are limitations as it is not an *in-vivo* model, but *in-vitro* analysis in a more controlled environment can be implemented. Whether the approach taken by the authors is applicable to other viruses as suggested by the results presented in the study has to be still investigated.

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