HHS Public Access

Author manuscript

Lancet Respir Med. Author manuscript; available in PMC 2020 May 21.

Published in final edited form as:

Lancet Respir Med. 2018 November ; 6(11): 805–806. doi:10.1016/S2213-2600(18)30245-5.

Cell culture keeps pace with influenza virus

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Cell culture is an essential component of biomedical research, and innumerable contributions to human health have originated from the manipulation of transformed cell lines propagated in a tissue culture dish. The more closely in-vitro cultures emulate human tissues, the more applicable these results are likely to be to human health; as such, efforts to move beyond transformed cell lines represent an active and important area of research. Primary cells obtained from human tissue, which are only capable of limited population expansion in vitro, can mimic human cell physiology, but can be laborious to isolate in the laboratory, expensive to purchase commercially, and variability exists between donors. Ex-vivo tissue biopsies or tissue models derived from human cells more accurately recapitulate the complexity of human tissue, but can be difficult for laboratories to obtain in addition to the limitations inherent among primary cells. Organoid cultures—stem cell-derived three-dimensional cultures that self-organise and self-renew ex vivo—have been shown to overcome these limitations by coupling the structure and function of human primary tissue cultures with the reproducibility and extended propagation capacity of transformed cell lines.[1]

Sachs and colleagues[2] reported the establishment of human airway organoids derived from human lung stem cells, which possess multiple epithelial cell types and numerous morphological characteristics (including mucus secretion, functional cilia, and distribution of sialic acid-linked glycoproteins) consistent with the human airway epithelium. In *The Lancet Respiratory Medicine*, Kenri Hui and colleagues,[3] assess the suitability of these organoids for the study of human and avian influenza viruses. The authors identify that airway organoids support influenza virus replication and induce host responses similar to those previously characterised in ex-vivo human bronchus explant cultures infected with influenza virus, a tool used in risk assessment algorithms.[4] Characterising alternative models to explant culture thus represents an important advance for in-vitro research, including, but not limited to, the study of influenza viruses.

The study by Hui and colleagues provides a strong foundation for subsequent studies using this ex-vivo system, which is likely to further understanding of influenza virus pathogenicity and tropism. The diversity of human and zoonotic influenza viruses associated with human infection warrants continued and expanded assessment in these systems,[4] and evaluation and

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The findings and conclusions are those of the author and do not necessarily reflect the views of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry. I declare no competing interests.

identification of molecular markers that contribute to heightened virulence of specific viruses in mammals. Better understanding of host responses will be key, and might be facilitated by the establishment of co-culture systems combining airway organoids with different immune cells that contribute to proinflammatory and other responses involved with cell signalling.[5] Modulation of inoculation conditions to more closely align with physiologically relevant human exposure routes and doses[6] might increase understanding of these properties.

Influenza viruses represent a principal respiratory pathogen in humans, often causing human infection following respiratory exposure, and respiratory illness following infection. Therefore, the generation of human airway organoids and characterisation of these cultures for use in influenza virus research represents an important step forward in this field. Concurrently, these advances highlight the need for similar development and characterisation of organoids derived from human tissue in other anatomical locations (both within and outside of the respiratory tract) that are implicated in human exposure to, and infection by, influenza viruses. To study the numerous exposure routes and disease manifestations associated with influenza virus infection,[7] a similarly expanded toolkit of in-vitro models is needed.

In-vitro experiments routinely support in-vivo examination of influenza virus pathogenicity, transmissibility, and tropism; these properties are multifactorial traits, and the use of mammalian models is crucial for a comprehensive evaluation of the complex virus-host interactions that occur after influenza virus infection. However, the refinement of tools used for cell culture is a necessary component of the three R's concept (reduction, refinement, replacement), which governs animal research.[8] Advancements in ex-vivo modelling, similar to those described by Hui and colleagues, can contribute to an enhanced understanding of data generated from mammalian models, and provide context and comparative information for ongoing efforts establishing ex-vivo cultures derived from other species, such as the ferret,[9] particularly with regard to influenza virus.

As influenza viruses continue to reassort and jump species barriers to cause human infection, parallel evolution and adaptation of the approaches used in the laboratory to study, characterise, and assess the potential pandemic risk of these novel and emerging strains must keep pace. The more closely laboratory culture models emulate human tissues, the better our understanding of the pathogens to which they are exposed will be. This report by Hui and colleagues, in addition to other recent advances in this area,[10] adds to a growing evidence base of organoids characterised for use in infectious disease research.[1]

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