Primary Cells and Respiratory Research

Respiratory research involves a huge array of conditions from chronic and acute dysfunction to infectious disease. Airway disease is caused by a broad range of factors from lifestyle and environmental damage like smoking and air pollution to individual genetics and the microbial milieu of the lung.

Certain diseases like tuberculosis are on the rise as bacteria become drug resistant, and as we've seen, new diseases such as coronavirus disease 2019 (COVID-19) represent a significant threat. The air liquid interface, as we will see below, is a unique biological niche requiring a cascade of processes to function correctly.

The lung is an extremely large yet delicate surface, vulnerable to damage by infiltrating particles and pathogens. The body has developed a complex array of defense mechanisms to prevent this damage, and the cells responsible rely on those around them to carry out these duties.

Cell culture allows study of a life-like model of biological processes with the freedom to manipulate and therefore better understand them. Cell lines go some way towards studying these processes, but significant issues with contamination and misidentification mean research with them is losing credibility. Primary cells represent an increasingly popular means to gain replicable results that are representative of the *in vivo* environment but are not without their own challenges.

Primary cells represent excellent models for studying respiratory disease in particular. Cell culture makes it possible to understand the mechanism of lung diseases at the cellular level and find useful targets within pathogenic processes.

Impact of Respiratory Disease

Respiratory disease has a huge impact on people's lives around the world. It is one of the biggest causes of reduced quality and length of life and health costs globally.

€380 billion/year total cost in EU

1/8th of total annual deaths in EU

>74k publications on respiratory disease in last 12 months

5.2 million disability-adjusted life years lost annually

>6 million hospital admissions anually

Key Respiratory Diseases

COVID-19
Over 2 million deaths worldwide*

Tuberculosis
1.4 million deaths annually

Asthma
334 million patients worldwide

Lung Cancer
1.6 million deaths annually

COPD
65 million sufferers worldwide – WHO predicts COPD will be 3rd biggest killer worldwide by 2030*

* Until February 2021 – https://covid19.who.int/

Cell lines

While cell lines represent the traditional means of studying lung disease, research using them is losing credibility due to significant issues with misidentification of cells used in research.

18–36%
of cell lines may be misidentified

>32K
research articles affected by misidentified cell lines

50%
of these since the year 2000

>500M
citations of research using misidentified cell lines

E.g.:
"'Lung cancer' cell line actually liver carcinoma cell line."
(Stacey, 2000)

E.g.:
"Research using 'human cell lines' actually rat cell lines."
(Masters, 2012)

Meaning
>17K
research papers using primary cells in the past year

Why primary cells?

Respiratory research benefits from primary cell research as this biological niche has a complex array of cells influencing and acting upon each other. 3D cell culture using primary cells from a disease specific donor allows understanding of *in vivo* processes in disease specific states, and comparison to healthy donor cells.

Challenges

- Need to isolate directly from tissue
- Finite lifespan
- Limited expansion capacity
- Require cell type specific growth media
- Limited donors
- Stringent quality control required to ensure replicability

Advantages

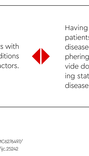
- Pre-characterized and ready to use
- Cells retain donor tissue characteristics
- Retain markers and functions seen *in vivo*
- Possible to model disease
- Can compare between donors and with cells from same donor
- Normal cell morphology

The challenges of primary cells are worth the potential benefits; replicable and accurate models mean time is saved on animal experiments or clinical trials based on inaccurate cell line results

3D cell culture

A key benefit of primary cells is the ability to carry out 3D cell culture.

Cells are trapped in a collagen gel matrix, replicating the *in vivo* scenario. Primary cells survive longer and act more like cells in vivo when cultured in a 3D environment.



E.g.: A 3D model of primary human adult lung cancer associated fibroblasts (LuCAFs) and human bronchial epithelial cells (HBECs) found HBECs are altered by LuCAFs via biochemical signals transferred through the biological matrix.

Air Liquid Interface (ALI)

The ALI is a unique cellular environment found in the respiratory system. To accurately study respiratory disease, cells must be in an environment which replicates this biological niche. High quality donor cells from disease specific donors are key to understand how the ALI is impacted by respiratory disease.

Healthy ALI

Sodium channels and water absorption appropriately inhibited, airway surface homeostasis maintained including correct mucus production and transport.

Cystic fibrosis ALI

Sodium channels unregulated, hyperabsorption of sodium and water and reduced pericilary liquid layer. Reduced mucus transport, acidic pH and increased reactive oxygen species contribute to pathological inflammatory milieu.

The Problem

Sourcing and characterization of physiological and pathological respiratory cells.

Access to donors with specific respiratory conditions or lifestyle factors.

The Solution

Streamlined tissue procurement with established partners, a wide variety of healthy and normal cells, consistency between batches.

Having access to COPD and asthma patients allows us to regularly source diseased cells that are crucial for deciphering relevant drug targets. We provide donor information (such as smoking status) vital for providing clues to disease progression.

References:

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