

Barrier Breakthroughs: Unmasking Microbial Invasion and Accelerating Precision Therapies

Wilflingseder Doris

Ignaz Semmelweis Institute, Interuniversity Institute for Infection Research, Vetmeduni Vienna, Austria

Emerging respiratory pathogens demand rapid, personalized testing pipelines grounded in physiologically relevant models. To meet this need, we established immune-competent, species-specific barrier systems - air-liquid interface airway epithelia, lung organoids, and other mucosal equivalents - augmented with tissue-resident myeloid cells to capture early host-pathogen interactions in human, and recently bat, equine, and porcine settings. Harmonized SOPs, defined quality control (QC) thresholds (transepithelial electrical resistance (TEER), junction and differentiation markers), and standardized readouts (qRT-PCR, infectious titers, high-content imaging, multiplex cytokine profiling) enabled reproducible, cross-model comparisons. Mechanistic analyses showed that complement opsonization and C5a - C5aR1 signaling modulate viral attachment, epithelial integrity, and myeloid activation, with context-dependent effects on interferon programs and chemokine gradients that shape permissiveness and inflammatory injury (1,2). Spatial profiling delineated epithelial-myeloid crosstalk and identified barrier states linked to viral restriction versus facilitation. A structured antiviral testing regimen assessed barrier-protective and attachment-blocking interventions, including ColdZyme (mucosal coating), plant-derived P80- and APS-based formulations, and the glycosaminoglycan mimetic enoxaparin targeting heparan-sulfate-dependent binding (3-6). Across models, these interventions reduced viral genome copies and infectious titers, preserved barrier metrics, and modulated innate responses, enabling rigorous head-to-head benchmarking. Together, these findings define a validated, cross-species pipeline that connects immune-epithelial mechanisms to therapeutic effects, providing a robust platform for comparative pathogenesis and rational evaluation of candidate prophylactics and treatments.

References

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