BA.5 Causes Higher Replication And Lethal Infection In K18-hACE2 Mice

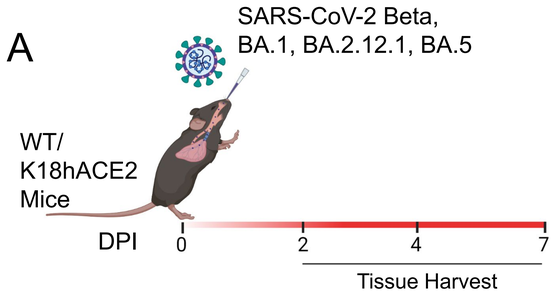
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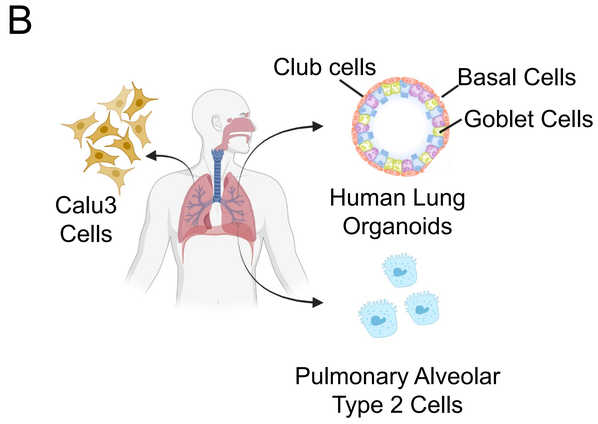
BACKGROUND

The continuous evolution of SARS-CoV-2 in the diverse immune landscape (natural, vaccine, hybrid) is giving rise to novel immune escape mutations. So far, the resulting new variants (BA.1, BA.2, BA.2.12.1) were observed to cause mild infections, however, BA.5 infections are associated with an increased risk of hospitalization. Therefore it is essential to investigate the pathogenesis of BA.5.

METHODS

Here we compared the pathogenicity of Pre-Omicron (Beta) and Omicron (BA.1, BA.2.12.1, and BA.5) variants in wild-type and K18-hACE2 mice. The virus replication kinetics was also studied in human Calu3 cells, pulmonary alveolar type 2 (AT2), and human airway organoids (HAO). Cell-to-cell spread of the virus was measured by syncytia formation assay and immunohistochemistry of infected lungs.





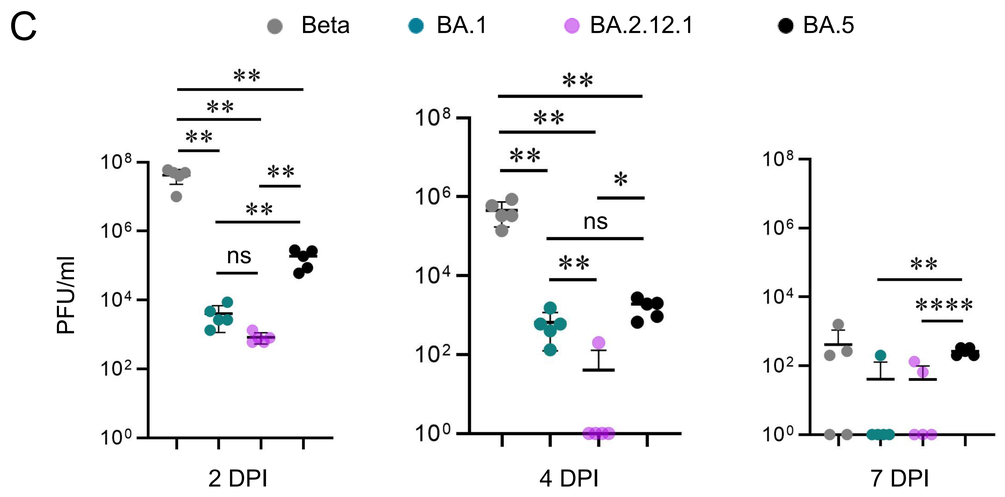
BA.5 replicates higher as compared to other Omicrons including BA.1 and BA.2.12.1.

lethal infection by BA.5 in K18hACE2 mice, may be attributed to its increased cell-to-cell spread and neurovirulence similar to pre-Omicron variants.

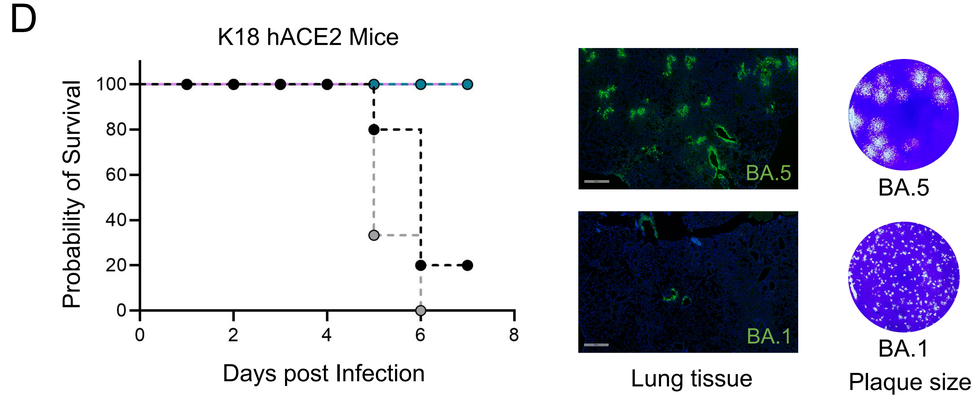
BA.5 replication is attenuated in pulmonary alveolar type 2 cells but not in the human airway or brain organoids

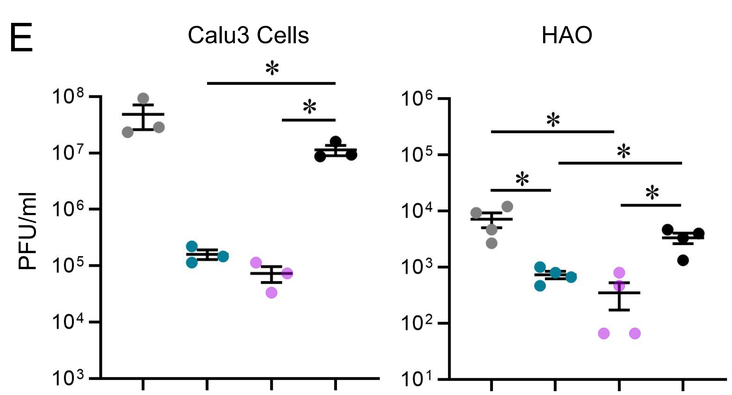
RESULTS

At the peak of virus replication, mature virus particle in BA.5 infected mice is significantly higher as compared to BA.1 and BA.2.12.1.



BA.5 infection is lethal to 80% of infected K18-hACE2 mice, however, wild type mice get moderate severity. SARS-CoV-2 Beta and BA.5 show comparatively higher cell-to-cell spread.





Calu3 cells and HAO show comparatively higher replication of SARS-CoV-2 Beta and BA.5. However AT2 cells were found to be resistant to BA.5 replication. BA.2.12.1 was found to replicate lowest among all the variants.

CONCLUSIONS

- The BA.5 variant (lineage) of Omicron has potential to regain the pathogenicity as it shows increased virulence compared to other Omicron sub-variants.
- Lethal infection of BA.5 in K18-hACE2 mice may be attributed to catastrophic encephalitis and increased cell-to-cell spread.

ADDITIONAL KEY INFORMATION

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