Secreted ORF8 Reprograms Macrophages to Enhance Lung Epithelial Cell Infection by SARS-CoV-2

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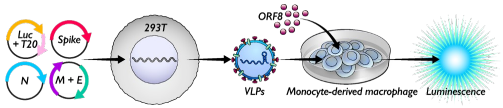
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BACKGROUND

- SARS-CoV-2 leads infected cells to produce a secreted accessory viral protein, **ORF8** that has been reported to interact with IL-17RA and is termed "Virokine."
- We investigated how ORF8 affects macrophages, and how macrophage infection affects lung epithelial cells.

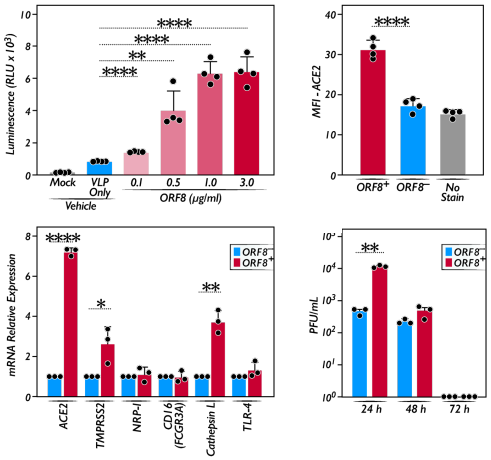
METHODS

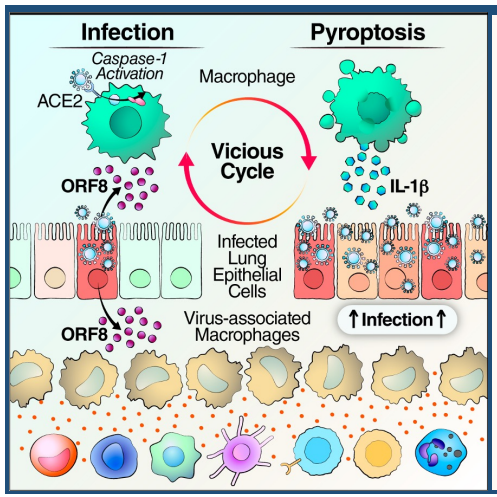
Monocyte-derived macrophages (MDM) and VLPs (Virus-Like Particles)



RESULTS

VLP uptake into macrophages is enhanced by soluble ORF8

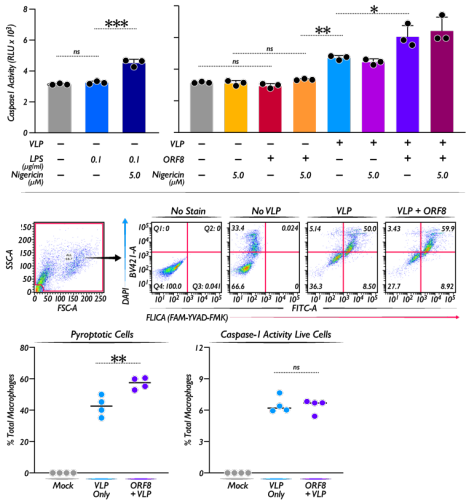




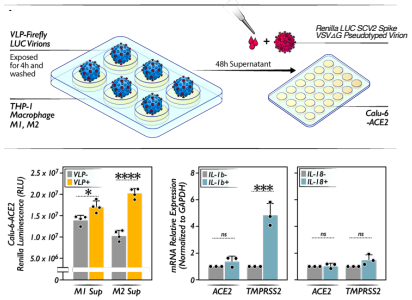
Highlights

- ORF8 enhances the expression of viral entry factors including ACE2 on macrophages
- ORF8 promotes the uptake of virions by macrophages, enhancing macrophage pyroptosis
- ORF8 induces a phenotypic shift from M1- to M2-like macrophages
- ORF8 boosts infection of lung cells in co-culture with macrophages and *in vivo* settings
- Anti-IL17RA suppresses ORF8-mediated enhancement of viral production

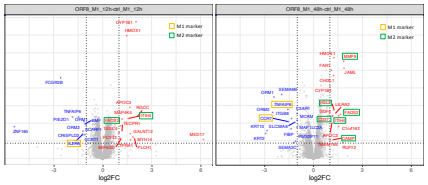
Extracellular ORF8 together with VLP uptake induces pyroptosis in macrophages

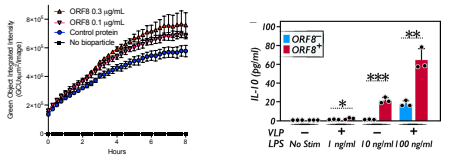


The supernatant of infected macrophages increases the susceptibility of pulmonary epithelial cells to infection

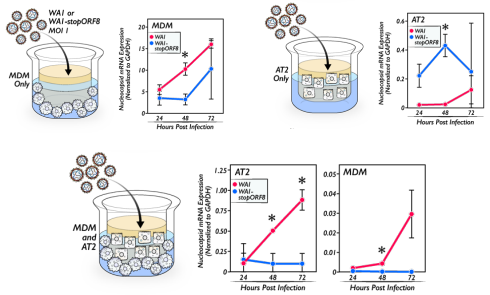


ORF8 transforms macrophage's phenotype

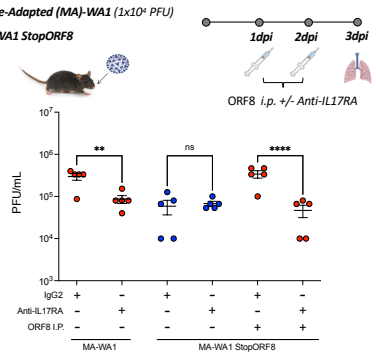




Viruses containing ORF8 enable SARS-CoV-2 to fully replicate in AT2 cells and macrophages



ORF8 enhances SARS-CoV-2 lung infection, inhibited by anti-IL17RA



CONCLUSIONS

ORF8 amplifies SARS-CoV-2 infection in lung epithelial cells by altering macrophage properties.

ACKNOWLEDGEMENTS

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