0231

Fc receptor-mediated infection of myeloid cells by SARS-CoV-2

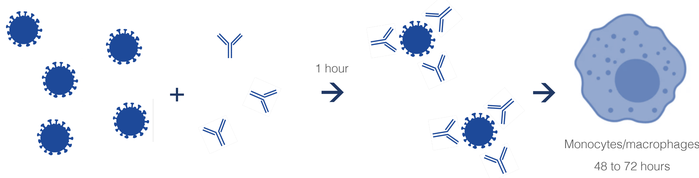
Suzanne Pickering[1], Harry D. Wilson [1], Enrico Bravo[1], Marianne R. Perera[1], Nathalia Almeida Dos Santos[1], Katie J. Doores[1], Michael H. Malim[1] and Stuart J. D. Neil[1]
[1]Department of Infectious Diseases, School of Immunology & Microbial Sciences, King's College London, London, United Kingdom

BACKGROUND

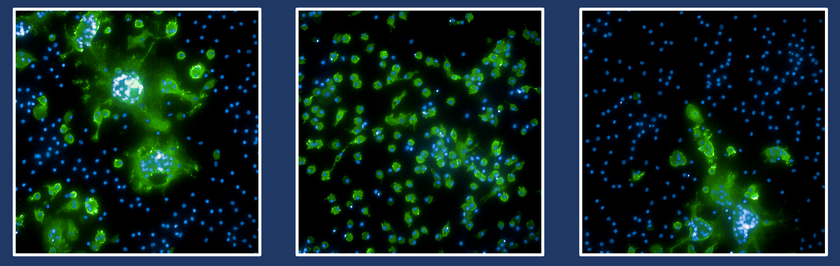
The role of myeloid cells in the pathogenesis of SARS-CoV-2 is well established, in particular as drivers of cytokine production and systemic inflammation characteristic of severe COVID-19. However, the potential for myeloid cells to act as *bona fide* targets of productive SARS-CoV-2 infection remains unclear.

METHODS

Using anti-SARS-CoV-2 mAbs with a range of neutralisation potencies and binding specificities, we performed a detailed assessment of mAb-mediated infection of monocytes and macrophages. THP-1 cells were used as a model system, with results confirmed in iPSC-derived and primary monocyte-derived macrophages.

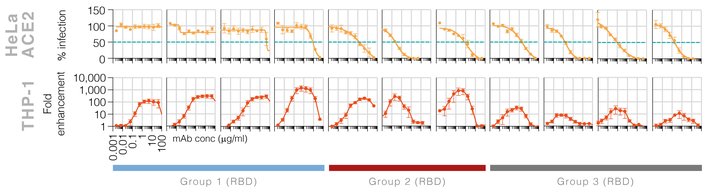


Monocyte-derived macrophages support **productive** replication of SARS-CoV-2 when infected via FcR-antibody interactions. Innate immune mechanisms limit viral replication and lead to the production of pro-inflammatory cytokines.

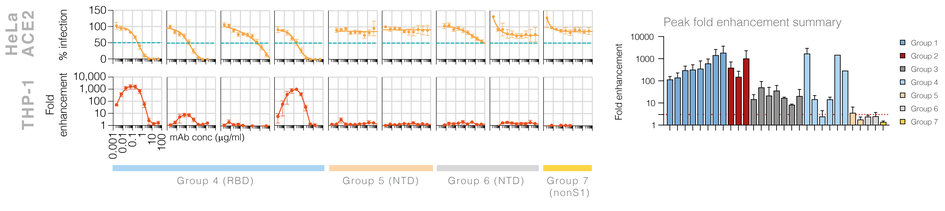


RESULTS

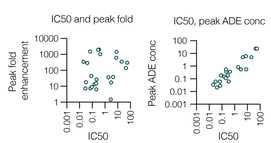
RBD-specific mAbs promote infection of monocytes at sub-neutralising concentrations



Infection of THP-1 cells was seen via mAbs targeting the spike RBD, but not with those targeting the NTD or S2 subunit. mAbs with the most consistent potential to mediate infection targeted a conserved region of the RBD (group 1/class IV).

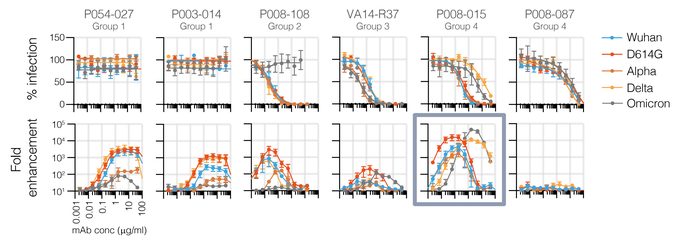


There was no correlation between the neutralising potency of the mAb and the ability to mediate infection, but there was a correlation between the IC50 and the mAb concentration that mediated peak infection.

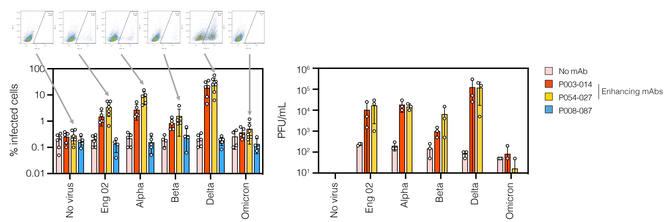


No infection of THP-1 cells was seen with the same quantity of virus but in the absence of antibody. Thus, antibody-FcR interactions are able to expand the tropism of SARS-CoV-2.

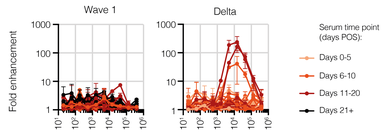
RBD-specific mAbs mediate THP-1 infection by other VOCs



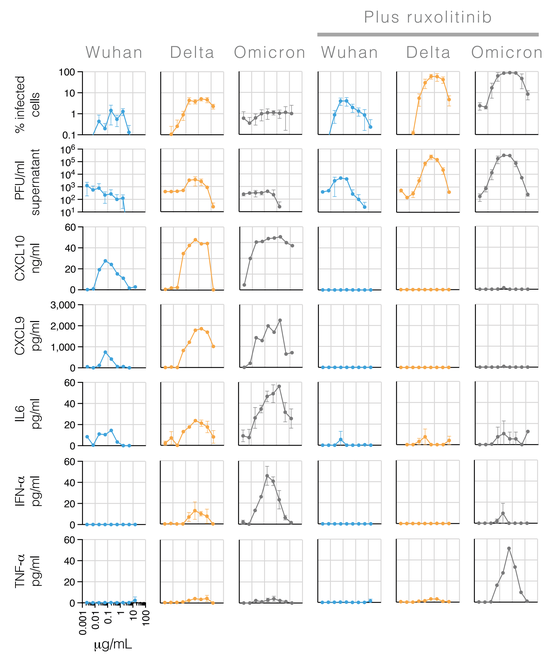
Studies with infectious virus demonstrate high-level and productive infection



Serum samples from primary infections mediate rare infection events upon dilution (n=3 of 80)



SARS-CoV-2 infection of primary monocyte-derived macrophages



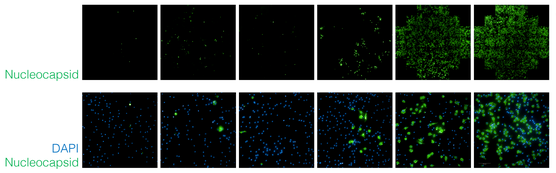
Studies were performed in primary monocyte-derived macrophages using Wuhan, Delta and Omicron virus (MOI=1) and the mAb P008-015.

Up to 6% of primary macrophages were infected. Addition of ruxolitinib, an inhibitor of JAK1/2 signaling, increased infection to up to 97% in the case of Omicron, revealing infection limited through innate immune mechanisms.

The production of pro-inflammatory cytokines correlated with infection levels.

NOTE: the same quantity of virus input is used in every condition. No infection is seen in the absence of antibody.

Images from peak infection for each condition:



CONCLUSIONS

Primary macrophages can be productively infected by SARS-CoV-2 via antibody-FcR interactions.

We hypothesise that a nascent antibody response during peak viral replication in primary infection presents a window of opportunity for myeloid cells to become infected, while establishment of a robust polyclonal response via vaccination or prior infection reduces the likelihood of this occurring. Infection via antibody-FcR interactions could contribute to pathogenesis in primary infection, systemic virus spread or persistent infection.