Restricted Infection of macrophages by SARS-CoV-2 Induces pro-Inflammatory Responses

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Abstract

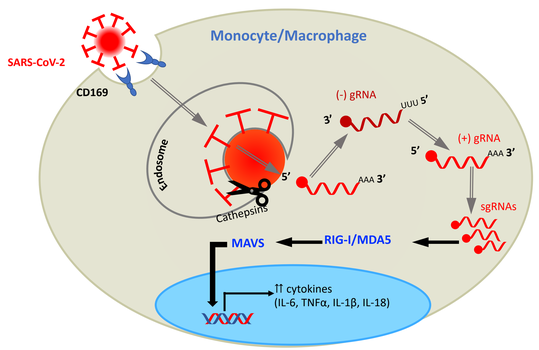
BACKGROUND: Persistent inflammatory immune response marked by pro-inflammatory cytokine expression is thought to be a major driver of chronic COVID-19 pathology. Although macrophages are not the primary targets of SARS-CoV-2 infection in humans, viral RNAs have been detected in activated monocytes/macrophages from post-mortem samples, which has been associated with hyper-inflammation in COVID-19 patients. In this study, we examined the role of CD169, a myeloid cell specific receptor, in facilitating SARS-CoV-2 infection, and its effect in inducing pro-inflammatory cytokines.

METHODS: Monocyte-derived macrophages (MDM) derived from purified human CD14$^+$ PBMCs, and PMA-differentiated THP1 monocytes were transduced to express ACE2 or WT/mutant CD169. Surface expression of was confirmed by flow cytometry. Macrophages were infected with authentic SARS-CoV-2 or S-pseudotyped lentivirus, and extent of virus replication and induction of proinflammatory responses determined by mRNA (qRT-PCR, smFISH), and protein analysis (immunofluorescence).

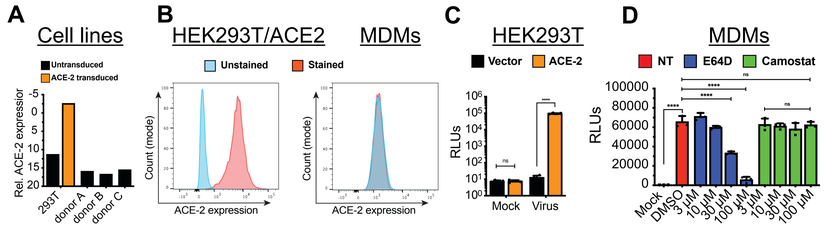
RESULTS: CD169-mediated SARS-CoV-2 entry in macrophages resulted in robust expression of viral genomic/sub-genomic RNAs, minimal viral protein expression, and no productive infection, suggesting partial or incomplete SARS-CoV-2 replication. Restricted expression of viral gRNA and sgRNA in CD169$^+$ macrophages elicited expression of pro-inflammatory cytokines (TNFα, IL-6, IL-1β, IL-18) in a RIG-I, MDA5 and MAVS-dependent manner, which was suppressed by remdesivir pre-treatment.

CONCLUSIONS: Collectively, our findings suggest that de novo expression of SARS-CoV-2 RNA in macrophages contributes to pro-inflammatory cytokine signature, and that blocking CD169-mediated ACE2 independent infection and activation of macrophages by viral RNA might alleviate COVID-19-associated hyperinflammatory response.

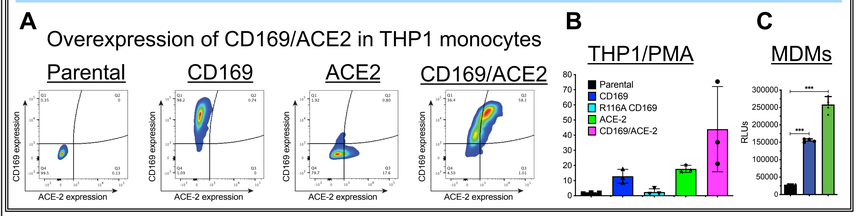
Model: CD169-mediated SARS-CoV-2 entry in human macrophages leads to expression of genomic and sgRNA viral RNAs, leading to RIG-I/MDA5/MAVS dependent innate immune activation and pro-inflammatory cytokine expression.



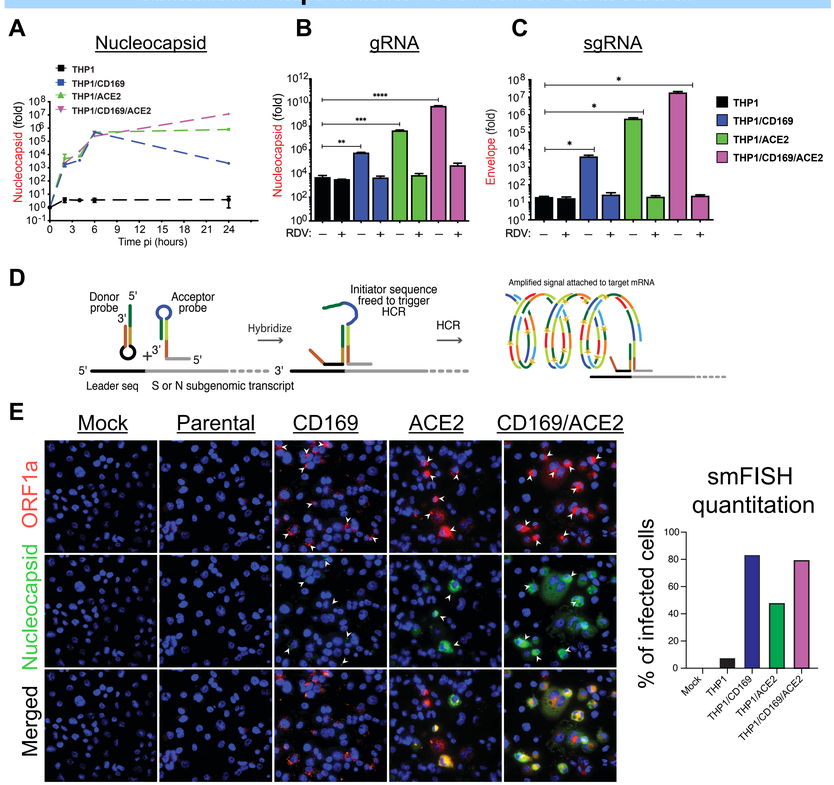
SARS-CoV-2 Spike protein can mediate ACE2-independent entry in macrophages



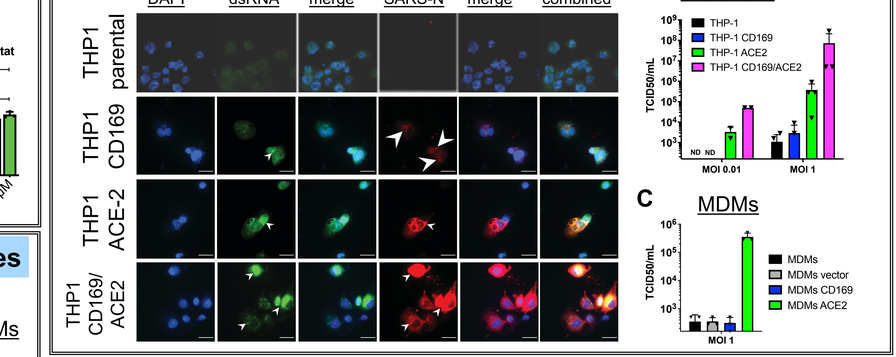
CD169 is a SARS-CoV-2 attachment/entry factor in macrophages



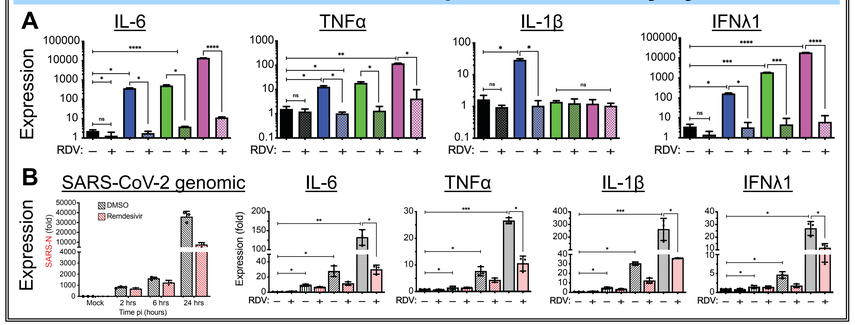
CD169-mediated entry of SARS-CoV-2 in macrophages facilitates expression of *de-novo* viral RNAs



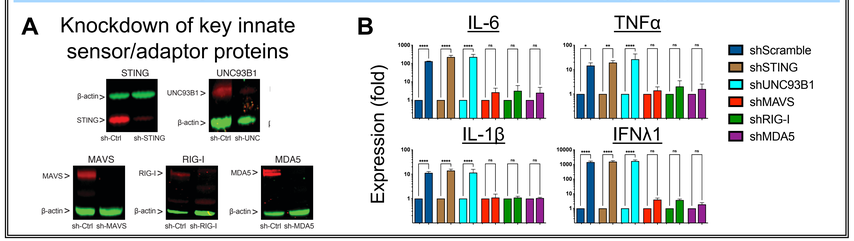
CD169 mediates abortive SARS-CoV-2 infection in macrophages



Low level expression of SARS-CoV-2 genomic and sub-genomic mRNAs is sufficient to induce pro-inflammatory cytokines



Sensing of SARS-CoV-2 RNA by RIG-I/MDA5 is required for MAVS-dependent activation of inflammatory cytokines



Conclusions

- CD169 facilitates SARS-CoV-2 entry in macrophage independent of ACE2
- Expression of *de-novo SARS-CoV-2* RNA induces inflammatory cytokines
- RNA-induced inflammation is blocked by RIG-I/MDA5/MAVS depletion

Acknowledgements

This work was supported by NIH grants R01AI064099, R01DA051889, R01AG060890 to S.G., and R01CA2 27292, R01AI 06036 to S.T and Y.B