TLR7 activation in M-CSF-dependent monocyte-derived human macrophages potentiates inflammatory responses and prompts neutrophil recruitment

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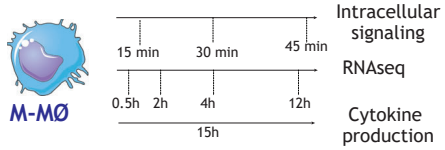
BACKGROUND

Toll-like receptor 7 (TLR7) is an endosomal Pathogen-Associated Molecular Pattern (PAMP) receptor that senses single-stranded RNA (ssRNA) and whose engagement results in the production of type I IFN and pro-inflammatory cytokines upon viral exposure. Recent genetic studies have established that a dysfunctional TLR7-initiated signaling is directly linked to the development of SARS-CoV-2-induced severe COVID-19. We previously showed that TLR7 is preferentially expressed by macrophages generated in the presence of M-CSF (M-MØ), whose MAFB-dependent transcriptome resembles pathogenic pulmonary monocyte-derived macrophage subsets in severe COVID-19.

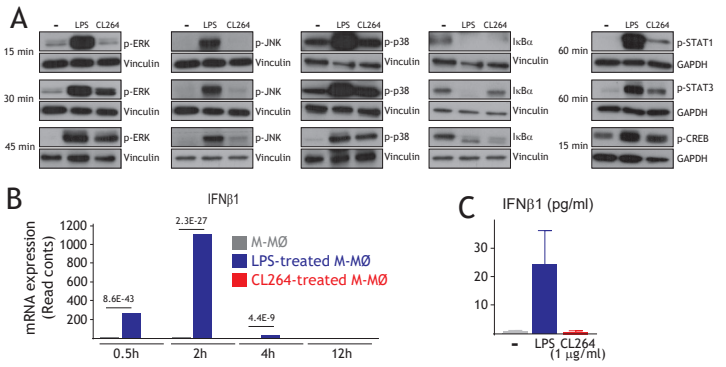
METHODS

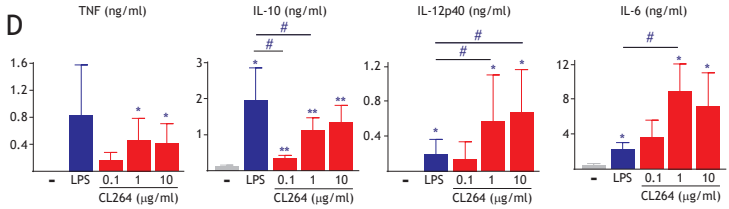
- *CL264*
- *LPS*
- *Untreated*



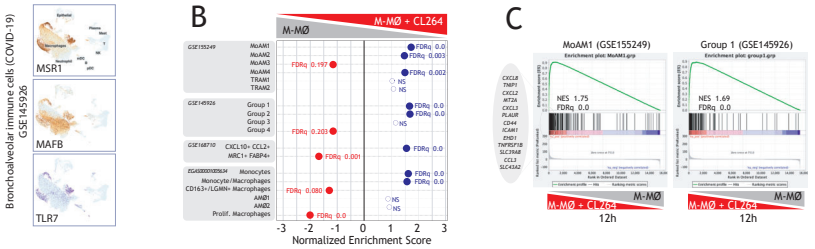
RESULTS

1- TLR7 activation in M-MØ triggers a weak MAPK, NFkB and STAT1 activation and leads to defective production of type I IFN

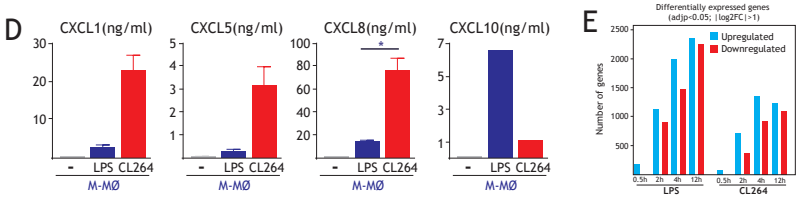




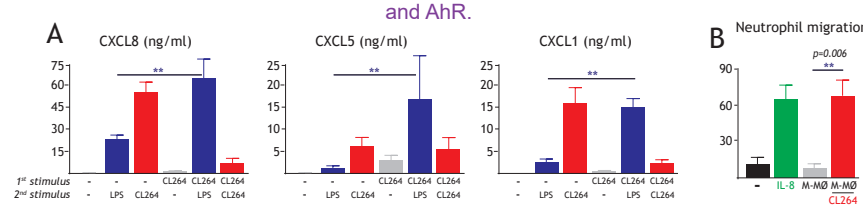
2- TLR7 engagement re-programs MAFB+ M-MØ towards a distinctive transcriptional profile. Specifically, TLR7-activated M-MØ acquired the expression of genes that characterize inflammatory macrophage subsets in COVID-19 and other inflammatory diseases, including genes encoding neutrophil-attracting chemokines (CXCL1-3, CXCL5, CXCL8) reported as biomarkers for severe COVID-19.

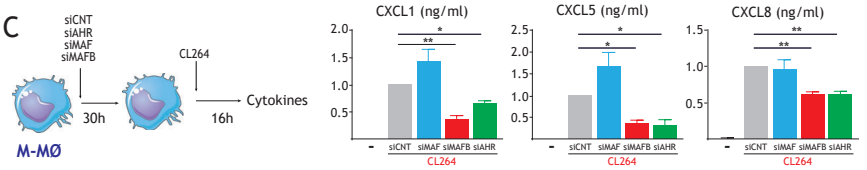


GSE145926: Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Liao M. et al.; *Nat Med 2020 Jun;26(6):842-844.*
GSE155249: Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. Grant R.A. et al.; *Nature 2021 Feb;590(7847):635-641.*
GSE145926: Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Liao M. et al.; *Nat Med 2020 Jun;26(6):842-844.*
GSE168710: IFN-γ and TNF-α drive a CXCL10+ CCL2+ macrophage phenotype expanded in severe COVID-19 lungs and inflammatory diseases with tissue inflammation. Zhang F. et al.; *Genome Med 2021 Apr 20;13(1):64.*
EGAS00001005634: SARS-CoV-2 infection triggers profibrotic macrophage responses and lung fibrosis. Wendisch D. et al.; *Cell 184:2021 6243-6261.e27.*

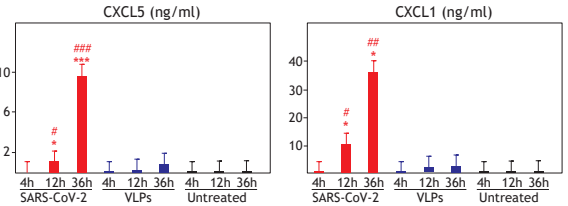


3- TLR7-activated M-MØ displayed enhanced pro-inflammatory responses towards secondary stimulation and a robust production of neutrophil-attracting chemokines (CXCL1, CXCL5, CXCL8), which was dependent on the transcription factors MAFB and AhR.





4- CXCL1 and CXCL5 release from M-MØ was also promoted by SARS-CoV-2 but not by Virus-like particles



CONCLUSIONS

As defective TLR7 signaling and enhanced pulmonary neutrophil/lymphocyte ratio associate with severe COVID-19, these results suggest that targeting macrophage TLR7 might be a therapeutic strategy for viral infections where monocyte-derived macrophages exhibit a pathogenic role.

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