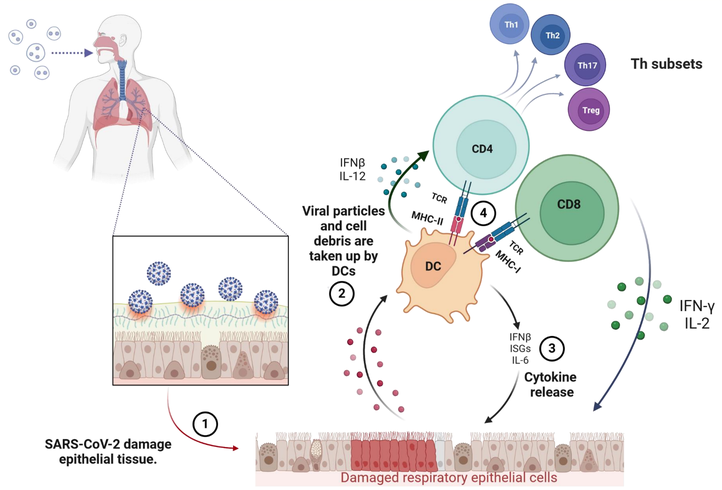
Complement-Driven Type-I IFN Response Enhances mTOR Activation and T-Cell Immunity

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Marta Bermejo-Jambrina[1,2], John L. van Hamme[2], Lieve van der Donk[2], Doris Wilflingseder[1], Teunis B.H. Geijtenbeek[2]
[1]Institute for Hygiene and Medical Microbiology. Medical University of Innsbruck, Innsbruck, Austria,
[2]Amsterdam UMC location-University of Amsterdam, Department of Experimental Immunology, Meibergdreef 9, Amsterdam, The Netherlands. Amsterdam institute for Infection and Immunity, Amsterdam, The Netherlands.

Background

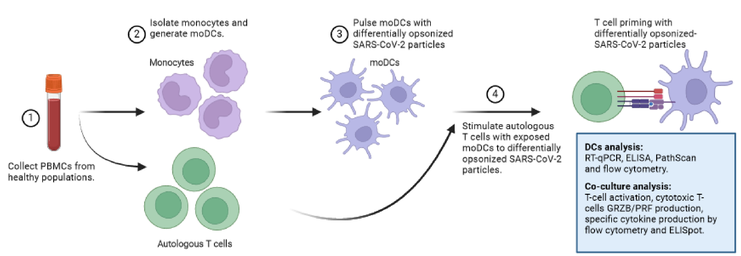


Uncontrolled SARS-CoV-2 infection leads to dysfunctions in both the innate and delayed adaptive immune systems. SARS-CoV-2 targets ACE2-epithelial cells in the respiratory tract. Dendritic cells (DCs), essential for guiding adaptive immune responses, do not express ACE2 and thus remain uninfected by SARS-CoV-2. The activation of DCs by SARS-CoV-2 and its role in local and systemic dysregulation remain unclear. Growing evidence suggests that DCs undergo aberrant maturation in COVID-19, which negatively affects T-cell activation.
Moreover, the dysregulation of the complement system is pivotal in various autoimmune, inflammatory diseases, and COVID-19. Despite its conventional role as central arm of innate immunity, the complement system equally influences adaptive immunity regulation.

Aim

Here we uncover an important role for complement in the induction of innate and adaptive immunity to SARS-CoV-2. Investigate the impact and mechanistic insight of complement on DC functionality and T cell priming in the context of SARS-CoV-2 infection.

Methods



- Type I IFN responses are pivotal to antiviral immunity by induction of innate resistance to virus replication but also activating cytotoxic T cell and T helper responses to viruses.
- Complement-opsonized SARS-CoV-2 induced expression of type I IFN and IL-1ß.
- Complement-opsonized SARS-CoV-2 enhances T cell proliferation and specific IFNγ/IL-2.

Our results indicate that complement-metabolism-NLRP3 axis regulates Th1 responses and plays and important role in T-mediated immunity.

Results

1. Complement induces DC activation and antiviral response via Akt-mTOR-NLRP3-caspase-1 axis.

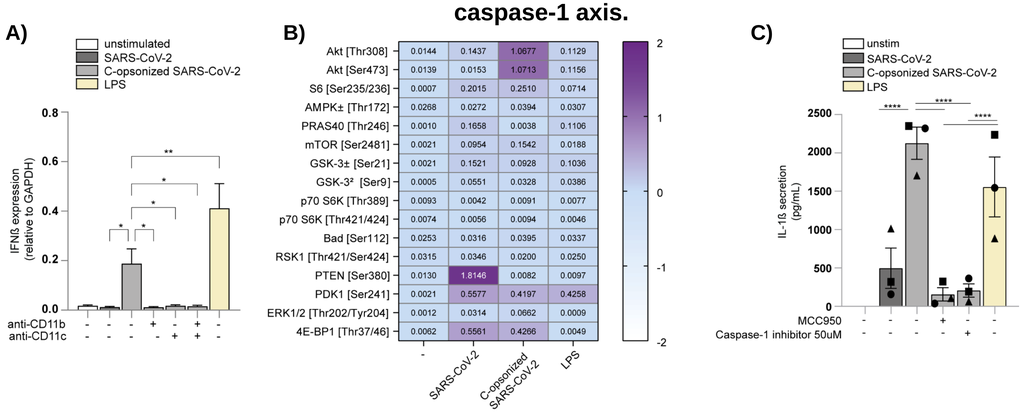


Figure 1: Exposure of DCs with complement-opsonized SARS-CoV-2 induces antiviral type I IFN, activates mTOR and IL1ß secretion.
(A) DCs were exposed to non- and complement-opsonized SARS-CoV-2 and mRNA was harvested at 2 hours after stimulation, for type I IFN. (B) DCs were exposed to non- and complement-opsonized SARS-CoV-2 and LPS and lysates were harvested at 4h for PathScan analysis.(C) DCs were incubated with MCC950 or with caspase-1 inhibitor for 2 h, followed by co-stimulation with non- or complement-opsonized SARS-CoV-2 and LPS. IL-1β secretion in the supernatant was measured after 24 h by ELISA

2. Complement induces CD4⁺ and CD8⁺ T cell proliferation and SARS-CoV-2 specific IFNγ/IL-2.

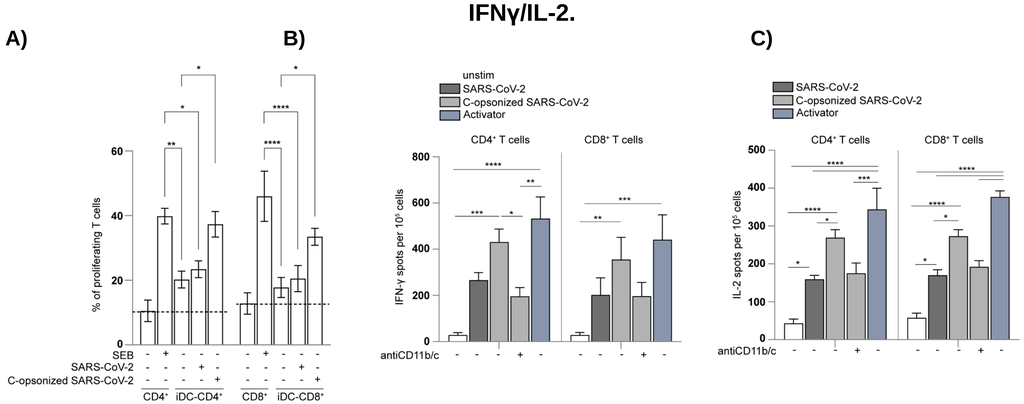


Figure 2: Complement-opsonized SARS-CoV-2 primed CD4+ and CD8+ T cells elicit anti-SARS-CoV-2 responses.
(A) Cultivating CFSE-stained PBLs in the presence of differentially opsonized exposed-DCs revealed complement opsonization to be capable increasing lymphocyte proliferation in both CD4⁺ and CD8⁺ T cells in comparison to the positive control, SEB. (B-C) DCs were stimulated with differentially-opsonized SARS-CoV-2 in presence or absence of anti-CD11b/c for 24h and co-cultured with T cells, CD4⁺ (B) and CD8⁺ (C). A control antigen T-cell epitope pool was used as positive control for 24h. IFN-γ and IL-2 secreting cells and expressed as spot forming cells were counted by ELISpot (n=5).

3. A complement-metabolism-inflammasome axis regulating Th1 response.

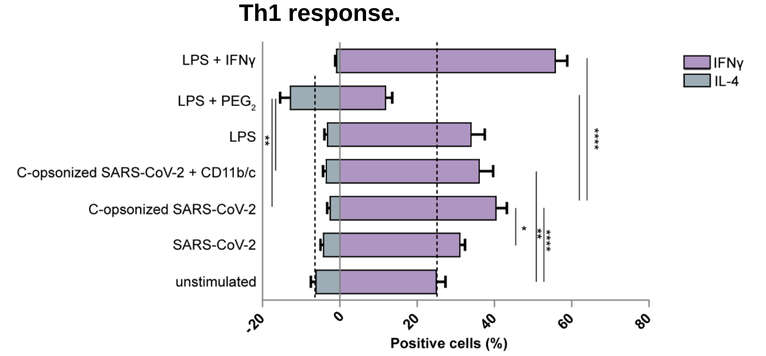


Figure 3: Complement-opsonized SARS-CoV-2 exposed DCs induce Th1 polarization in vitro.
CD4⁺ T cell polarization into Th1 and Th2 in response to SARS-CoV-2 and complement-opsonized SARS-CoV-2.

Conclusions

Our results show that SARS-CoV-2 does not trigger DCs. Exposure of complement-opsonized on DCs leads to a strong innate and adaptive immune responses. These findings suggest that non opsonized SARS-CoV-2 could have an escape mechanism, whereby improper activation of DCs could result in aberrant adaptive immune responses in COVID-19 patients. Notably, complement-mediated DC trigger can potentially be used as an adjuvant in therapeutic strategies, allowing for sensing of the virus by the host DC, followed by an adequate antiviral immune response.

Correspondence and funding

marta.bermejo@i-med.ac.at
Institute for Hygiene and medical Microbiology
Medical University of Innsbruck

m.bermejojambrina@amsterdamumc.nl
Department of Experimental Immunology
Amsterdam UMC, location AMC
Amsterdam Institute for Infection and Immunity



ÖAW Österreichische Akademie der Wissenschaften
ZonMw
Amsterdam UMC University Medical Centers
Amsterdam institute for Infection and Immunity