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# Lung-resident, M2e-specific CD4 T cells critically protect during influenza infection

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Torsdagen den 13 December, klockan 1300

av Ajibola Omokanye

Fakultetsopponent:
Professor Sarah Gilbert
Jenner Institute, University of Oxford

**Avhandlingen baseras på följande delarbeten**

I. M2e-tetramer-specific memory CD4 T cells are broadly protective against influenza infection.
Eliasson DG, Omokanye A, Schön K, Wenzel UA, Bernasconi V, Bemark M, Kolpe A, El Bakkouri K, Ysenbaert T, Deng L, Fiers W, Saelens X, Lycke N.
*Mucosal Immunology. 2018; 11(1):273-289.*

II. Single-cell transcriptome analysis of lung-resident, M2e-specific T cells identifies cytotoxic sub-populations that rapidly expand to control influenza virus replication.
Omokanye A, Lebrero C, Ågren R, Proux-Wéra E, Ong LC, Kolpe A, Bernasconi V, Wenzel UA, Schön K, Bemark M, Saelens X, Lycke N.
*Manuscript*

III. Lung-resident, M2e-specific CD4 T cells act synergistically with NP-specific CD8 T cells to confer improved protection from influenza infection.
Omokanye A, Ong LC, Bernasconi V, Strömberg A, Schön K, Saelens X, Lycke N.
*Manuscript*

**SAHLGRENSKA AKADEMIN**
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# Lung-resident, M2e-specific CD4 T cells critically protect during influenza infection

**Ajibola Omokanye**

Avdelning för Mikrobiologi och Immunologi, Institutionen för Biomedicin, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2018.

**Abstract**

Memory $CD4^+$ T cells are a critical component of the adaptive immune response to fight infection. However, current vaccines against influenza only focus on the other arm of adaptive immunity—triggering B cells to produce antibodies. These antibodies are directed against viral surface proteins that are extremely heterogeneous and rapidly mutate, meaning that current vaccines offer neither broad protection against different strains, nor long-term protection as a result of mutation. In this thesis we aim to develop a mechanistic understanding of how memory $CD4^+$ T cells directed against the conserved influenza protein, M2e, mediate protection in a mouse model of immunisation and infection.

We administer M2e intranasally within an adjuvant vector, CTA1-DD, which enables us to generate large populations of M2e-specific $CD4^+$ T cells in lung. Having identified the critical recognition sequence for the M2e peptide, we established an MHC class II tetramer assay that enables detection, extraction and characterisation of M2e-specific $CD4^+$ T cells from the lungs and lymphoid tissues of immunised mice. In paper 1, we utilise in-vitro antigen restimulation and flow cytometry to broadly characterise these lung-resident $CD4^+$ T cells as having a predominantly Th17 phenotype. We identify that their capacity to protect mice from different strains of influenza virus is independent of antibody, by using knock-out and congenic mouse models. In paper 2, we identify that intranasal delivery is critical for generating lung-resident $CD4^+$ T cells, and confirm that tissue-resident memory cells do not require support from circulating cells during infection. We also characterise the M2e-specific $CD4^+$ T cell population further by profiling their transcriptome at the single-cell level during the time-course of infection. We identify a previously unreported cytotoxic population of M2e-specific $CD4^+$ T cells that rapidly expand to control virus propagation during the early phase of infection. Characterisation of this subset is of significance to the influenza vaccine field, where the search for correlates of $CD4^+$ T cell mediated protection have thus far yielded no robust biomarkers. In paper 3, we show how M2e-specific $CD4^+$ T cells can work synergistically with $CD8^+$ T cells targetting another conserved influenza protein to confer improved protection from influenza infection. Together, these findings highlight the critical role played by M2e-specific $CD4^+$ T cells in protection from influenza, underlining its usefulness as a component of future universal vaccine candidates.

**Keywords**: influenza, vaccine, universal, heterosubtypic, M2e, CD4, Th17, ThCTL, tissue-resident, cytotoxic, single-cell RNA-seq.

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