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RESEARCH HIGHLIGHT

Targeting MAIT cells as a cellular adjuvant for humoral immunity: a new player in a very old game

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Twenty years ago, a seminal paper identified MR1 as the critical antigen presenting molecule for mucosal-associated invariant T (MAIT) cells.[1] Since then, there has been an ever-growing effort to elucidate the biology of MAIT cells and to identify ways in which they can be harnessed. A recent paper by Pankhurst *et al.*, led by the laboratory of Dr Lisa Connor at the Victoria University of Wellington, demonstrates that experimental delivery of a strong MR1 ligand can serve as an adjuvant to induce antibody responses against a co-delivered protein antigen.[2] These data provide proof-of-concept that MAIT cells can be specifically targeted for vaccine purposes and adds yet another aspect to the growing list of MAIT cell functions.

Mucosal-associated invariant T cells are a unique population of T cells that express an invariant T cell receptor and have conserved biology across individuals and between species, which allows them to functionally bridge adaptive and innate immunity.[3] They are a promising target cell population for translational applications for several key reasons. Firstly, unlike conventional MHC molecules, MR1 is non-polymorphic and thus presents the same antigen epitopes across all people and non-human animals.[4] The antigens presented by MR1 are non-peptide in nature and are primarily metabolic intermediates of the riboflavin (vitamin B2) biosynthesis pathway – a biosynthesis pathway broadly found in many microbial species but not in higher organisms. This allows MAIT cells to recognize many bacterial and fungal pathogens.[5] Secondly, MAIT cells are present at high frequencies in many human tissues (~3–4% of blood or lung $CD3^+$ T cells), which makes them hyper-abundant relative to any given antigen-specific T cell population. Finally, MAIT cells exit the thymus as pre-differentiated memory cells, which allows for rapid effector functions in response to stimulation.[6] Combined, these traits make MAIT cells particularly appealing targets as a cellular adjuvant to boost vaccine immunogenicity.

To investigate this proposition directly, Pankhurst and colleagues employed intranasal delivery of recombinant protein combined with 5-A-RU (5-amino-6-D-ribitylaminouracil) and methylglyoxal (MG), which spontaneously forms the potent MAIT cell ligand 5-OP-RU (5-(2-oxopropylideneamino)-6-D-ribitylaminouracil). Stimulation with 5-A-RU + MG led to activation of lung MAIT cells. Co-administration of the model antigen ovalbumin with the MAIT cell ligand triggered germinal center B cell responses in the lung-draining lymph nodes (LNs). This translated into the induction of both serum and mucosal antibody responses against ovalbumin as well as the influenza virus HA protein and SARS-CoV-2 spike proteins when these were the co-administered antigen (Figure 1). Critically, these vaccine-induced responses could protect in a lethal influenza challenge model.

Through a series of elegant mechanistic studies, the authors demonstrate that migratory dendritic cell (DC) populations in the lung are activated and traffic to the draining LNs (Figure 1). This activation is dependent on the CD40 signaling axis, which is a canonical pathway of T cell-mediated activation of DCs.[7] While the authors speculate that these migratory DCs are activated within the lung, where MAIT cells are quite abundant, it is also possible that DCs are activated by MAIT cells within the LN after trafficking into this tissue. Regardless, this matured DC population then primes T follicular helper (T_{FH}) cells, which are critical for promoting B cell and antibody responses (Figure 1).[8]

Several studies have related anti-bacterial antibody titers and levels of MAIT cell activation in human cohorts.[9,10] However, it remains unclear whether this reflects a causal role for MAIT cells in promotion of antibody responses or a correlation with overall immune activation. Activation of MAIT cell activation *in vitro* can also induce antibody secretion,[11] but until recently, direct

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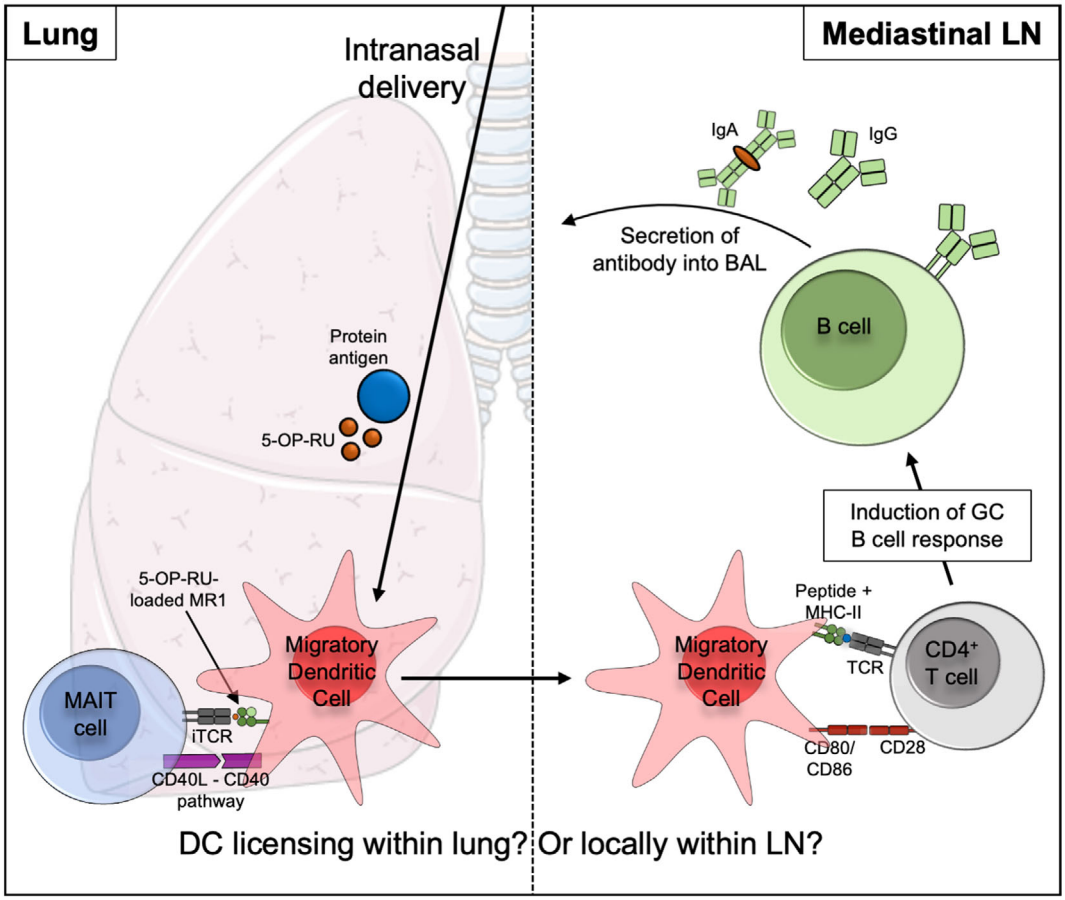

Figure 1. Proposed mechanism of immune induction by vaccination with a protein + MAIT ligand formulation. Intranasal vaccination with a formulation containing recombinant protein and a MAIT cell ligand (5-OP-RU) results in uptake by migratory dendritic cells (DCs). These migratory DCs present 5-OP-RU *via* MR1 to activate MAIT cells, which signal back to the DC *via* CD40L to induce maturation. Within the draining lymph node (LN), migratory DCs present peptide antigen on MHC class II and co-stimulatory molecules to naïve T cells, inducing their priming and differentiation into T follicular helper (T_{FH}) cells. In turn, T_{FH} cells provide critical help signals to naïve B cells and thereby support the formation of a germinal center B cell response. This ultimately results in antibody-secreting cells that produce vaccine antigen-specific IgA and IgG present within the lung. 5-OP-RU: 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil. Lung tissue cartoon from smart.servier.com under a CC BY 3.0 license.

evidence that this occurs *in vivo* was lacking. However, in 2022, a study described a population of MAIT cells that had phenotypic characteristics of T_{FH} cells, including expression of CXCR5, ICOS and PD-1.[12] These cells appeared to be capable of enhancing antibody responses to *Vibrio cholerae* infection, by a mechanism that was not directly defined. The current study looked for but did not identify any such $MAIT_{FH}$ cells following vaccination, instead MAIT cells acted much more akin to a conventional T_{FH} cell to induce DC maturation and thereby trigger T_{FH} cell responses (Figure 1). Given these two potential distinct mechanisms of enhancing B cell responses, it will be of interest to determine the relative contribution of direct $MAIT_{FH}$ function compared with DC licensing in the response to bacterial pathogens.

Induction of mucosal antibodies by vaccination has been a topic of substantial interest particularly in the context of COVID-19, where they are believed to play a critical role in protection from infection. The currently licensed COVID-19 viral vector and mRNA vaccines do not induce strong mucosal responses.[13,14] Thus, the reported induction of mucosal IgA antibodies by the protein +5-A-RU/MG vaccination regimen is particularly promising for the translational relevance of these findings. One aspect of the reported vaccine regimen that remains unclear is how translatable it is to other routes of administration. In the study, intranasal administration was used, which is the most relevant for the induction of antibodies in the lung. However, the frequency of MAIT cells in the lungs of laboratory

mice is also higher than in most other tissues.[15] Thus, it is unclear whether delivery into the lung is a specific requirement for the efficacy of this vaccine regimen possibly due to MAIT cell frequency, the presence of a migratory DC population, or both. Further studies will be required to investigate.

While the data presented on protein +5-A-RU/MG vaccination are a very exciting proof-of-concept, a few major translational questions remain. In the current study, antibody titers were measured only 1 week after the final vaccine dose and the durability of antibodies produced by this vaccine was not assessed. Additionally, the vaccine regimen consisted of three doses of vaccine at 14 day intervals. The relative contribution of repeated short-interval dosing needs to be determined. Interestingly, a recent study examining malaria vaccine-induced antibody responses found a clear benefit of extending the interval between protein + adjuvant immunizations.[16] This may be of relevance to the current protein +5-A-RU/MG regimen as well.

In closing, the current work by Pankhurst and colleagues reveals new biology for MAIT cells and opens new translational research avenues to pursue. The process of MAIT cells activating DCs *via* CD40 signaling to drive T_{FH} cell development and ultimately to the induction of antibodies is an exciting new frontier of MAIT cell biology, with potential relevance to many infection and disease settings.

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AUTHOR CONTRIBUTIONS

Nicholas M Provine: Conceptu alization; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

I declare no conflicts of interest.

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Graphical Abstract

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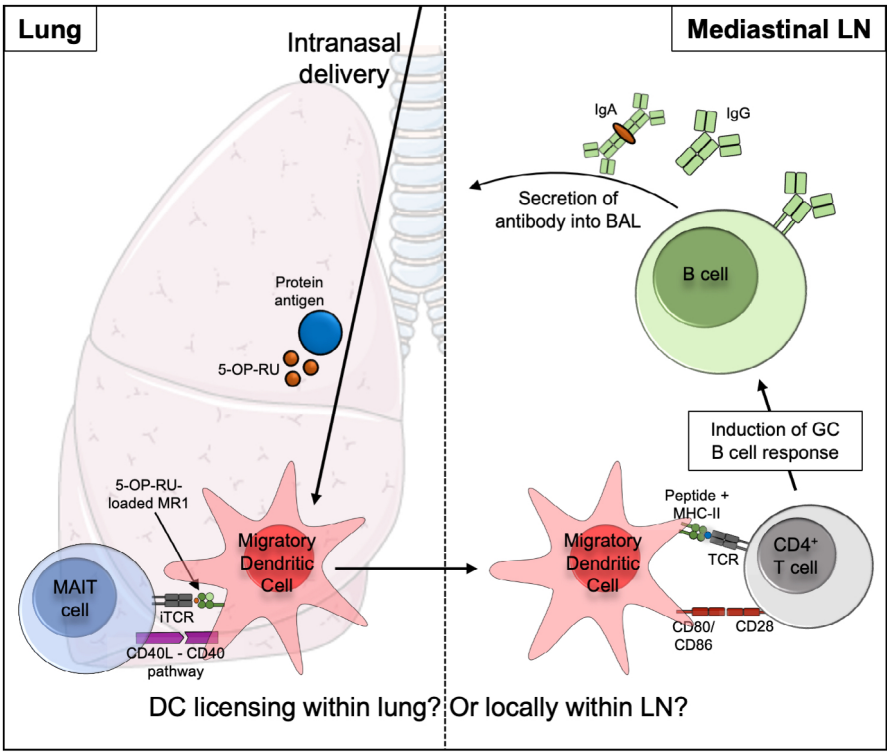

In this article, I discuss recent work by Pankhurst *et al.* They found that MAIT cells can serve as a cellular adjuvant to boost immunity to a protein adjuvant. Intranasal co-administration of protein antigen with a strong MAIT cell ligand results in the the production of mucosal IgA and IgG antibody responses. This process is driven by MAIT cell-mediated maturation of migratory dendritic cells.