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**ICB NEWS AND COMMENTARY**

**Title:**

# Friends help make lasting memories

Strapline

Inflammatory monocytes promote resident memory T cell persistence following lung infection

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CD8$^+$ Resident memory T cells (Trm) "sound the alarm" to initiate the recruitment of multiple innate and adaptive cells following local, secondary challenge[1]. A new study just published in *Immunology & Cell Biology* now demonstrates that Trm may also get a little help in order to be maintained in the periphery[2].

*Partitioning of T cell memory*

Following infection, the acquisition and maintenance of T cell memory is essential to confer protection. Pathogen-specific CD8$^+$ T cells can differentiate into diverse memory cell subsets[1]. These broadly segregate into three distinct populations; effector memory cells (Tem) which circulate throughout the body; central memory cells (Tcm) that primarily locate in lymph nodes, and tissue-resident memory cells (Trm) which are defined by their location in peripheral tissues[1]. Given their strategic positioning at sites of pathogen entry, Trm represent the first T cell contact during recall responses and act to coordinate local secondary responses[3-5]. Understanding the lineage relationships between the different CD8$^+$ T memory cells and factors that govern memory CD8$^+$ T cell fate are crucial to develop better therapies against cancer and viral infection as well as to design more efficient vaccination strategies.

In this issue of *Immunology & Cell Biology*, Desai *et al.* use CCR2-deficient mice, to investigate the role of inflammatory monocytes (IMs) on CD8$^+$ T cell effector and memory responses in the lung following vaccinia virus infection[2]. IMs were shown to be expanded in the spleen and lungs following infection, and this was dramatically reduced in CCR2-deficient animals. This loss of IMs did not affect the initial differentiation of T cell effectors or the establishment of either circulating or Trm memory cells. However, 50 days following infection, CCR2$^{-/-}$ mice had a specific loss in the CX3CR1$^-$CXCR3$^+$ memory population. Desai *et al.* used intravenous labeling of CD45 to determine that this compartment comprised of both circulating and resident memory, and that both of these were decreased in CCR2$^{-/-}$ hosts. This analysis also permitted discrimination of other Tem and Trm populations within the lung. CXCR1$^{int}$ memory CD8$^+$ T cells have the highest self-renewal capacity and are the predominant subset in peripheral tissues[4, 6]. Desai *et al.* show that this population also consists of both patrolling and resident T cell memory, however these were unaffected by loss of CCR2. How unique populations of Trm individually contribute to secondary

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responses is not well understood. This current study provides a new model to dissect individual roles of Trm populations and how they contribute or compensate to immune protection.

*The helpers of Trm differentiation and maintenance*

Recently, cDC1 dendritic cells, which specifically express Clec9A (DNGR-1) were shown to be required for Trm priming and differentiation[7]. Clec9A-mediated cross presentation is specifically required for Trm priming within draining LNs. Interestingly, these interactions were not essential for formation of circulating T cell memory[7]. During T cell priming, $CD4^+$ T cell help also assists Trm differentiation[8]. In the absence of $CD4^+$ T cells help, $CD8^+$ T cells express high levels of T-bet, which hinders Trm differentiation. Further, the lower T-bet levels expressed in the presence of help, in turn induce expression of CD103 on Trm, facilitating their correct localization in the lung[8, 9]. Finally, once formed, neutrophils provide a trail of CXCL12 which leads memory CD8 cells to the lung[10]. This current study adds IMs to the team of cellular players that assist the differentiation, trafficking, positioning, and maintenance of Trm (Figure 1).

*How might IMs influence Trm persistence?*

The expression of CXCR3 on the $CX3CR1^-$ Trm population is of interest for their maintenance as memory $CD8^+$ T cells are recruited into nasal-associated lymphoid tissue (NALT) through CXCR3 signaling[11]. It is tempting to speculate that without specific cell contacts or cytokines keeping them sequestered in the lung, $CX3CR1^-CXCR3^+$ Trm may migrate to into alternative locations, such as the NALT.

The precise mechanism by which IMs regulate the persistence of Trm in the lung warrants further investigation. Desai *et al.* show that IM cell numbers decrease in the lung by day 20 following infection. This timing is prior to Trm contraction in $CCR2^{-/-}$ mice, suggesting direct interaction between IM and Trm is not required. However, as the $CX3CR1^-$ compartment was comprised of both circulating and resident memory, IMs may co-localize with Trm at other sites which then replenish lung Trm. Indeed, others have shown co-localization between IMs and intestinal Trm influences their survival and persistence[12]. Further, adoptive transfer experiments of $CCR2^+Ly6C^+$ monocytes show that this population can differentiate into DCs or macrophages in the inflamed lung[13]. Therefore, it may be either of these cell types, which were not identified by Desai *et al.* that promote Trm persistence. The visualization of the distinct memory populations within their niche would greatly inform

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memory $CD8^+$ T cell subsets biology and clarify the requirement for cell contact and the cellular players that drive retention. As Desai *et al.* study suggests, the helpers of Trm are likely different for each Trm subtype and different again at unique peripheral sites.

IMs may also influence the local inflammatory cues that are required for Trm maintenance. Several studies have shown the cytokines IL-7, IL-15, IL-18 and TGFβ are important for Trm long-term persistence[1, 9, 12, 14]. Of these, IM can rapidly produce bioactive IL-18 and IL-15 following infection, although how much is produced at steady state or following pathogen clearance is unknown[15]. Further, as IL-15 is required for initial Trm priming, if IMs were the cellular source at this time, the phenotype of CCR2-deficient mice would be more pronounced early in infection[7, 9].

While further studies are needed to elucidate the mechanisms by which IMs influence Trm maintenance, this intriguing study by Desai *et al.* highlights the importance of cell collaboration for long-term persistence of memory.

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**Figure 1**. The friends of Trm priming, recruitment and maintenance. (**a**) In draining LNs, antigens are cross presented to Trm via Clec9a by cDC1s in the presence of $CD4^+$ T cells. (**b**) This induces expression of CD103 allowing recruitment to peripheral tissues. Neutrophils lay a trail of CXCL12 to promote T cell recruitment into the lung. (**c**) Within the lung inflammatory monocytes (IM) promote the retention of CX3CR1- Trm potentially through direct contact or cytokine secretion. Thus, multiple cells work together to establish and maintain Trm cells.

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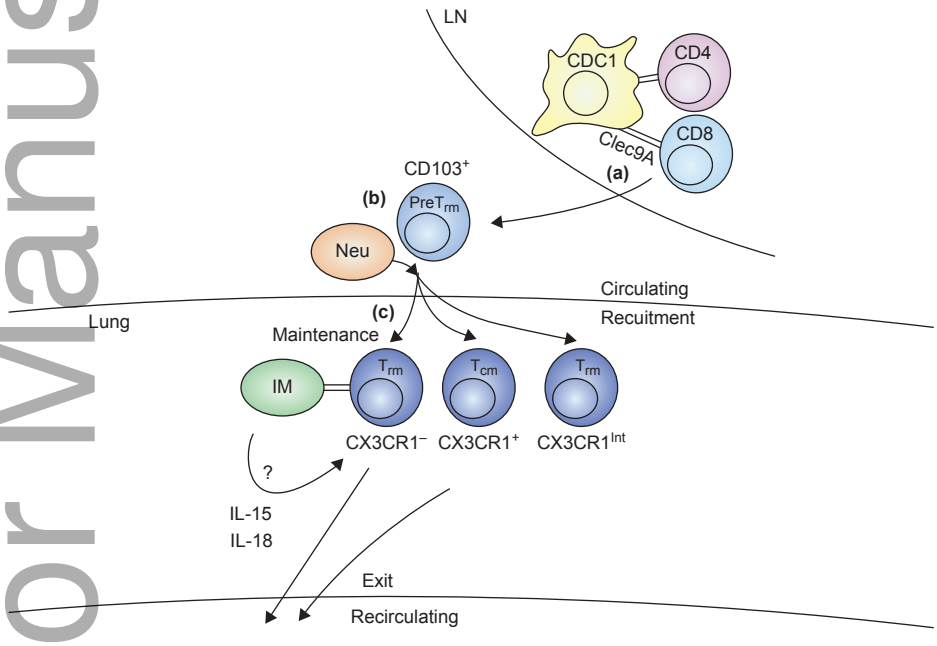


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