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RESEARCH HIGHLIGHT

Mobilizing forces - CD4+ helper T cells script adaptive immunity

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Traditionally, $CD4^+$ T cells have been understood to play a key role in 'helping' $CD8^+$ T cells undergo efficient activation and proliferation in response to foreign pathogens. This has been thought to be directed primarily by $CD4^+$ T cell interactions with dendritic cells (DCs) [1, 2] that convert 'unlicenced' DCs into DCs capable of implementing a full blown immune response ('licenced' DCs). More recently it has emerged that even when $CD4^+$ T cell help appears not to be essential for the first wave of effector 'killer' cytotoxic $CD8^+$ T lymphocytes (CTL) to fight infection, it is crucial in order for killer $CD8^+$ T cells to acquire the ability to form memory cells capable of protecting the body [3-5]. In a further extension of the importance of $CD4^+$ T cells, a paper recently published in *Nature* by Nakanishi *et al*. [6] now paints an even broader picture of the pivotal role of $CD4^+$ T cells in laying the foundation of the immune response. In an unexpected twist, Nakanishi *et al*. [6] found that it was $CD4^+$ T cell signals that provide the roadmap to guide effector $CD8^+$ T cells to infected tissues where they can destroy infected cells.

Immune responses against pathogens depend in part on the generation of fully differentiated 'killer' (or effector) and memory $CD8^+$ T cells. $CD8^+$ T cells differentiate into effector and memory cells following the recognition of antigenic peptides loaded onto class I Major Histocompatibility Complex (MHC) molecules displayed on the surface of specialized antigen presenting cells (APCs) called DCs. In addition, $CD8^+$ T cells need to receive 'costimulatory' signals to differentiate into fully functional effector and memory cells. This can be provided either by direct ligation of the costimulatory receptors with their ligands expressed on the surface of DCs, or by soluble factors secreted mainly by DCs and 'helper' $CD4^+$ T cells. This process is necessary to form protective memory $CD8^+$ T cells that are able to survive for long periods of time in the body poised to rapidly respond to a second encounter with the foreign pathogen.

The concept of $CD4^+$ T cell help initially emerged from studies demonstrating that successful priming of CTL depends on the presence of $CD4^+$ T cells. These studies partitioned the need for helper functions based on the level of inflammation driving the immune response. Weak inflammatory settings such as allograft transplantation, challenge with model antigens or poorly replicating virus (such as herpes simplex virus (HSV)) infection that induce minimal tissue damage were considered to require $CD4^+$ T cell help ('helper-dependent') to ensure the full complement of signals that would normally be provided in an intensely inflammatory response. Precisely what those signals are has been less clear. One widely accepted model centres on the ability of helper $CD4^+$ T cells to 'license' DCs for $CD8^+$ T cell priming. This process depends on the interaction of the costimulatory receptors, such as CD40 expressed by the DC, and CD40L (CD154) expressed by $CD4^+$ T cells (Figure 1) [1, 2]. Once DCs have been modified in the licencing process (e.g. induction of maturation) they are then able to efficiently convert naïve $CD8^+$ T cells into fully competent cytotoxic T cells. Cognate recognition of the same DC-displaying antigen by the $CD4^+$ and $CD8^+$ T cell is necessary to complete this "ménage à trois" [7]. By contrast, CD4 help appears to be redundant in situations where viruses, such as influenza, induce sufficient inflammation providing licencing signals most likely through Toll-Like Receptor activation of DCs [8, 9]. We, and others, extended this concept of CD4 help when it was discovered that $CD4^+$ T cells not only were important for initial priming of helper-dependent $CD8^+$ T cell responses, but also played a critical role in programming $CD8^+$ T cell memory development (Figure 1) [3, 5, 10].

$CD4^+$ T cells are a strategic target for several viral pathogens (including human immunodeficiency virus). By

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focusing on this cell type, these pathogens have been able to cripple effective anti-viral immunity and gained a significant advantage in establishing persistent infection. One mechanism by which the virus might evade the $CD8^+$ T cell response could be attributable to $CD4^+$ T cells simply failing to prime $CD8^+$ T cells to be effective killers through poor DC licencing. The study presented by Nakanishi *et al*. [6], however, suggests a new dimension where $CD4^+$ T cells play a role in actually hard-wiring the homing machinery of effector $CD8^+$ T cells, distinct from the signals induced in the licensing process. Without this, effector $CD8^+$ T cells cannot correctly localize to and kill virally-infected cells. In a mouse model of genital HSV-2 infection, Nakanishi *et al*. [6] asked whether part of the helper function of $CD4^+$ T cells is to guide activated $CD8^+$ T cells to the effector site (the vaginal mucosa) where they can deliver their lethal blow to virally-infected cells. They elegantly show that the cues provided by $CD4^+$ T cells to ensure efficient effector $CD8^+$ T cell recruitment depend mainly on the IFN-γ secreted by $CD4^+$ T cells at the effector site itself. This, in turn, switches on the expression of the chemokines CXCL9 and CXCL10, which forms a chemotactic gradient within the vaginal microenvironment (potentially mediated by the vaginal epithelial cells). $CD8^+$ T cells primed during HSV-2 infection express high levels of the chemokine receptor CXCR3, and this enables them to rapidly respond to the

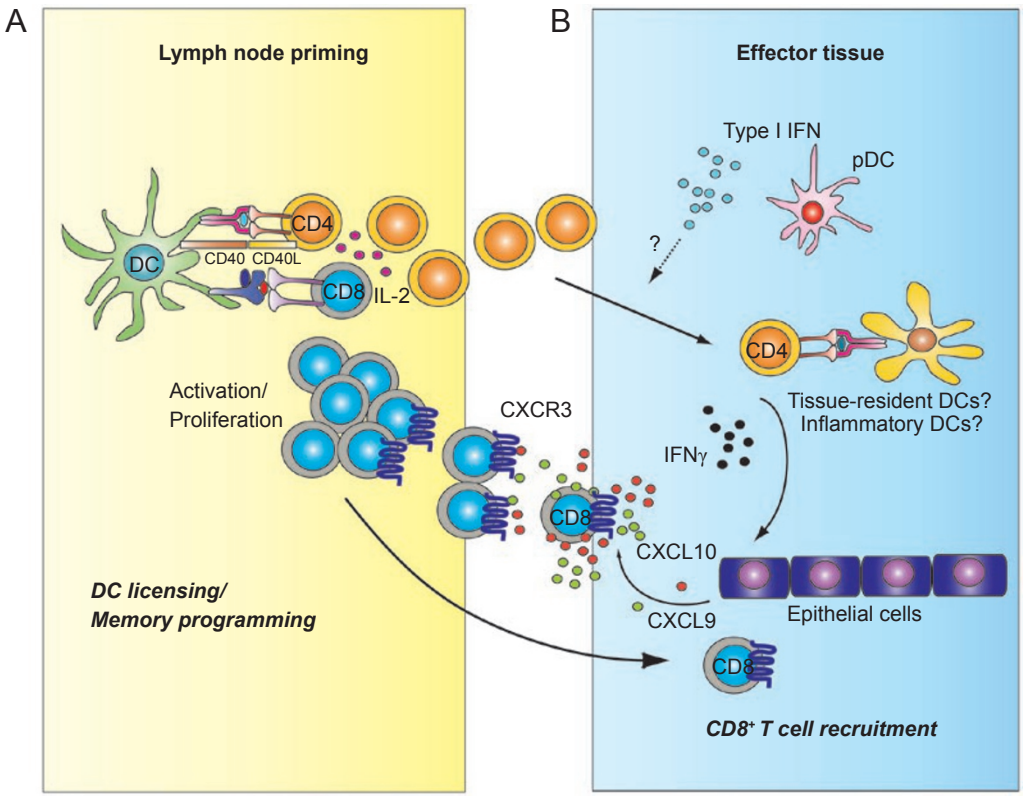

Figure 1 The multi-dimensional roles of $CD4^+$ T cell 'help' orchestrate $CD8^+$ T cell immune responses beyond licencing DCs in the lymph node. **(A)** DC licencing/programming. Mucosa-derived DCs migrate to the lymph node draining the site of infection and mature by upregulating costimulatory molecules and MHC class II-antigen complexes so they can activate naïve T cells. $CD4^+$ T cells 'license' LN-resident DCs through complementary interactions between CD40L and its receptor CD40. This leads to the full maturation of the DCs which are then capable of efficiently priming naïve $CD8^+$ T cells. Activated $CD4^+$ T cells synthesize an array of cytokines including IL-2 that are critical to optimally initiate the antigen-specific $CD8^+$ T cell differentiation program allowing the formation of potent effector and memory cells, which must then find their way to the effector site, spleen or other non-lymphoid tissues. These cytokines can also potentially recruit additional cell types critical to the immune response into the lymph nodes. **(B)** Instructional recruitment to the effector site. Activated $CD4^+$ T cells migrate to the effector site guided by components of the inflammatory milieu (perhaps including type I IFN) and interact with local APCs (such as tissue-resident DCs or inflammatory DCs) displaying MHC II molecules loaded with pathogen peptides. This interaction leads to secretion of IFN-γ by activated $CD4^+$ T cells and in turn switches on the secretion of the chemokines CXCL9 and CXCL10 by epithelial cells. The resultant chemokine gradient guides cytotoxic $CD8^+$ T cells expressing the chemokine receptor CXCR3 to the effector site where they can destroy pathogen infected cells.

chemokines CXCL9 and CXCL10 and efficiently migrate to the infected tissue (Figure 1).

This work raises several important questions about precisely how key players in the immune response are directed to coordinate the immunological stage. A central finding of this study is that temporal localization of $CD4^+$ T cells to the infected vaginal tissues preceded the migration of $CD8^+$ T cells. The key mechanisms regulating $CD4^+$ T cell recruitment and subsequent retention at the effector site were not addressed in the current study. It seems likely that this would depend critically on the placement or recruitment of DCs loaded with MHC class II/viral peptide complexes. The secretion of IFN-γ by $CD4^+$ T cells within the infected vaginal mucosa indicates that $CD4^+$ T cells have very recently engaged local APCs carrying viral peptides on MHC class II molecules. The nature of the APCs driving IFN-γ production by $CD4^+$ T cells has not been investigated but they are most likely to be tissue-resident DCs (such as those that express the surface molecule CD103) [11] or inflammatory DCs recruited to the effector site. Indeed, ablation of inflammatory DCs in a simulated reactivation model of HSV-1 suggested that they were critical for activation of effector $CD8^+$ T cells [12]. An alternative proposition that parallels the role of $CD4^+$ T cell-derived cytokine driving recruitment of $CD8^+$ T cells is that specific DC subsets producing cytokines may drive the sustained influx of $CD4^+$ T cells while conventional DCs present viral or pathogen antigens. Nakanishi *et al*. [6] showed that in the absence of type I IFNs signaling, the critical influx of $CD4^+$ T cells into the vagina was impaired implying that type I IFNs was a key player in the process. One subset of DCs, the plasmacytoid DC (pDC), is an important source of type I IFNs in inflamed peripheral tissues. pDCs are considered to be essential to some viral infections, but the function of pDC-derived IFNα has not been determined. Perhaps pDCs participate in optimizing $CD4^+$ T cell recruitment through liberation of IFNα.

In conclusion, the study of Nakanishi *et al*. has uncovered a new dimension to the $CD4^+$ T cell 'help' paradigm. For the first time, they show that $CD4^+$ T cells not only impact on $CD8^+$ T cell differentiation during the priming phase, but can also modify the effector site microenvironment to ensure more efficient $CD8^+$ T cell recruitment. This raises the issue of whether $CD4^+$ T cells might have a broader role in modifying their microenvironment, not only during the effector phase but earlier during the priming phase, by promoting an inflammatory microenvironment. A broader investigation of the role of $CD4^+$ T cells in immune cell recruitment to both lymphoid and non-lymphoid tissues during different types of infections, i.e. "CD4 dependent" vs "CD4 independent", will be essential to fully understand how CD4 help orchestrates $CD8^+$ T cell immune response to infections.

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