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Mini Review

The role of CD4 T cell help for CD8 CTL activation

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ABSTRACT

CD4 T cells play an important role in the initiation and persistence of CD8 T cells responses. In this review, we report on and evaluate the mechanisms by which CD4 T cells contribute to activation of CD8 T cells and the signal pathways of the down-streaming events after CD4 T cell help.

CD8 CTL cells are essential for protection against viruses, intracellular bacteria infection and tumor cells. Understanding the mechanism for CTL activation, survival and long term maintenance has become one focus for many immunologists. Numerous studies in recent years have reached a consensus that CD4 T cell help is essential for CD8 CTL priming. The help provided by CD4 T lymphocytes during the priming of CD8 T lymphocytes confers a key feature of immune memory: the capacity for autonomous secondary expansion following re-encounter with antigen. Once primed in the presence of CD4 T cells, helped CD8 T cells acquire the ability to undergo a second round of clonal expansion upon restimulation in the absence of T cell help. The CD8 T cells that are not helped by CD4 T cells, in contrast, can mediate effector functions such a s cytotoxicity and cytokine secretion upon restimulation, but do not undergo a second round of clonal expansion [1,2]. These disparate responses have features of being programmed, that is, guided by signals that are transmitted to naïve CD8 T cells during priming, which encode specific fates for their clonal progeny. In this regard, exploring the instructional programme that governs the secondary response of CD8 T cells has significant impact on the future design of CD8 CTL based vaccination. This paper will discuss the mechanisms of CD4 T cell help, the DC licensing model and the downstreamevents following CD4 T cell help pathway.

The mechanisms of CD4 T cell help

CD40–CD40L signaling pathway

Recent findings have established a DC licensing model. In this model, the CD40L expressing CD4 T cells can interact with the professional APC-DC through the CD40–CD40L pathway. This interaction can lead to the activation/licensing of DC, then the licensed DC can activate CD8 CTL cells. This model was originally proposed/established by 3 papers in Nature in 1998 [3–5]. In those studies, they found that CTL response was dependent on both CD40 and CD40 ligand and that in the absence of CD4 T helper cells an agonistic antibody to CD40 can substitute for CD4 T cell help. Since the APC was the only known cell to express CD40 and CD4 T helper cells were known to express CD40 ligand upon activation, it was concluded that CD40-dependent licensing of APC was the crucial nature of CD4 T cell help. This proposed licensing model was seriously challenged by another study recently in Science [6]. In this study, the authors could show that CD4 T cell help for the differentiation of CD8 T cells into memory T cells can occur even when all APCs are CD40-deficient. They showed that CD8 T cells can express CD40 transiently after activation. Moreover, CD40-deficient CD8 T cells can never differentiate into memory cells, even in the presence of CD4 T helper cells. They cannot receive helper signals from antigen specific CD4 T cells. Thus, as B cells, the helper signals required for differentiation of CD8 T cells into memory cells appear to pass through the CD40 molecule expressed by activated CD8 T cells. In this model, although CD4 T cell help is CD40-dependent, it is through a direct contact between CD4 T cells and CD8 T cells. The role of DC in this case is to provide the chance that CD4 T cells

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and CD8 T cells can be put into proximity for their contact. Thus this study gave direct challenge to the proposed licensing model. Lee and colleagues demonstrated that optimal CD8 CTL response to influenza is dependent on CD40 signaling. However, both primary and secondary response to influenza require CD40 expression on non-T cells [7]. Thus in this case, CD4 T helper cells do not activate CD8 T cells directly through CD40 signaling. With this study, they could show that the direct interaction between CD4 T cells and CD8 T cells through CD40–CD40L signaling is not a universal mechanism for CD4 T cell help. Schuurhuis and colleagues further explored this proposed model. They showed that the DC cell line D1 could activate CD8 CTL with the help of CD4 Th cell [8]. However, when the D1 cells were stimulated with agonistic anti-CD40 Ab, they can activate CD8 CTL in a CD4 T cell-independent way, thus further suggesting this DC license model might be true. In 2004, a Nature Immunol paper further gave direct in vivo evidence for DC licensing by Th cells [9]. In this study, they could show that the in vivo sorted DC, only when they were licensed by CD4 T cells, could mediate a memory T cell response. Thus, this model of licensing of DC by CD4 Th cells for CTL priming was finally firmly established.

IL-2

One important characteristic of CD4 T cells is that they can produce multiple cytokines. Thus cytokines have lone been suggested that they can be the mediators of CD4 T cell help. In vitro studies have found that IL-2 is essential for the effective generation of CTL response when helper T cells and CTL were combined in the culture flask [10]. However, conflicting results exist since CTL response to viruses can be generated in IL-2 knock out mice [11]. More recently, using a graft versus host disease model, it was found that the ability of CD4 T helper cells to produce IL-2 was essential for sustained expansion of alloreactive CTL [12]. Using a cross-priming model, several recent studies have demonstrated that the absence of CD4 T cell help for CD8 CTL priming can be overcome by the provision of exogenous IL-2, thus establishing the role of IL-2 for CD4 T cell help [13,14]). More studies need to be done in order to confirm the role of IL-2 as the helper of CD8 CTL or this role can only exist in some certain cases.

IFN-γ

IFN-γ is one of the most important type 1 cytokines. It has been shown that IFN-γ can enhance the cytotoxicity of CTL in addition to being one of the important effector arms for CD8 CTL. In a recent report, Wolchok and colleagues demonstrated that in a DNA vaccination model, the CTL is fully dependent on CD4 T cell help. However, this CD4 T cell-dependent CTL is lost in IFN-$\gamma^{-/-}$ mice. It can be restored when recombinant IFN-γ was injected in vivo at the priming stage [15], suggesting IFN-γ is the essential mediator for CD4 T cell help in this model. A more recent study by Kumaraguru et al. used the well characterized HSV and OVA model system. They found that the helper function of CD4 T cells is mainly mediated by IFN-γ producing CD4 Th cells but not IL-2 producing CD4 Th cells [16]. Thus the role of IFN-γ as CD4 helper function has been implicated but needs more explorations in the future.

Other mechanisms

The CD40-independent CD4 T cell help has also been demonstrated. Pardoll et al. used both in vivo and in vitro CTL priming system to demonstrate that the CD4 T cell help in their model is CD40-independent. They found the help signal is mediated by direct contact of CD4 T cell with the APC [17]. The nature of this contact mediated signal was not identified. It has been reported that signaling of osteoprotgerin ligand (OPGL), another TNF-receptor family member expressed by DC has some similar effects to CD40 signaling. In other words, CD4 T cells can interact with DC through the TRANCE (tumor necrosis factor-related-activation-induced cytokine) pathway which finally leads to the activation of DC [18,19]. Also the CD4 T cells can acquire the effector function for virus protection in this case. Thus TRANCE has been documented as a signaling pathway leading to CD4 T cell activation independent of CD40L [20]. But the use of this signaling pathway by helper cells involved in CTL induction has not been reported. It's tempting in the future to explore whether this pathway is also used by CD4 T cells for CD8 CTL priming independently of CD40 pathway.

The downstreamevents of CD4 T cell help: what happens to DC and CD8 T cells following CD40 ligation?

So far, the most characterized and accepted model is still the CD4 Th cells, DC, CD8 CTL model and CD40–CD40L pathway is the major signaling pathway between CD4 Th cells and DC. One important problem would be to address what happened to DC after CD4 T cell licensing so that DC can activate CTL?

IL-12

The major cellular subset responsible for IL-12 production in vivo is mature DC. It has been shown that IL-12 is a key regulator of CD8 CTL response in vitro and in vivo [21]. Thus it would be interesting to explore that whether IL-12 is the downstreamevent following DC maturation by CD40 ligation. Bianchi et al. reported that immunization of DC pulsed with a class I binding tumor peptide failed to elicit CD8 CTL response unless it was treated with anti-CD40 agonistic Ab before immunization. They further demonstrated that neutralization of IL-12 during CD40 activation in vitro can abrogates the adjuvant effect. The addition of exogenous IL-12 can overcome the requirement for anti-CD40 activation Ab [22,23]. Thus IL-12 might be a significant downstreamsignal for DC after CD40 ligation. However, using the classical OVA Ag, it also has been shown that DCs derived from IL-$12^{-/-}$ mice pulsed with OVA peptide are fully capable of mounting a robust CD8 CTL response which is CD4 T cell and CD40L dependent [24]. Thus it seems that IL-12 is not required for the full activation of CD8 CTL in this CD4 T cell and CD40L dependent model. However, IL-12 neutralization or repletion was not used in this study. Also, the nature of Ag may decide different mechanisms. Further future studies need to link this discrepancy in different models.

B7–CD28 signaling

One important characteristic of DC maturation after CD40L activation is that DC can up-regulate the expression of the costimulatory molecules. Examining the costimulatory pathways might identify the pathway between DC and CD8 CTL which can finally lead to CTL activation. B7–CD28 pathway is one of the most important costimulatory pathways. Using a cross-priming model, it has been reported that both CD28 and B7-1/B7-2 are required for CD40-activated APC to cross prime CTL [25]. The priming by CD40 activated APC was prevented by blockade of CD28. However augmenting CD28 signals with an agonistic Ab can bypass the requirement for CD4 T cell help or CD40 activation. They also found that blockade of the negative regulatory B7 receptor CTLA-4 failed to prime CTL in the absence of CD4 T cell help. Thus this study supports the up-regulation of B7 molecules on APC leads to increased CD28 signaling and a commitment to cross-priming of CD4 T cell dependent CTL.