ELSEVIER

Local development of effector and memory T helper cells

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Clonal evolution underpins all facets of adaptive immunity. In particular, antigen-specific helper T (Th) cell development is central to high-affinity B cell immunity and protective vaccination. Dendritic cell maturation and TCR affinity-based selection mechanisms control the recruitment and effective propagation of preferred antigen-specific Th cell cohorts in local lymphoid tissue. Importantly, follicular B helper T (T_{FH}) cells emerge as the specialized local effector Th cells that orchestrate the stepwise development of B cell immunity in these local environments. Recent studies also introduce the role of persistent antigen in the development of effector Th cells with evidence for long-term antigen depots that might contribute to local antigen-specific Th cell memory.

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Introduction

Foreign antigen triggers innate immunity and clonal selection mechanisms that drive the evolution of adaptive immunity. In the context of pathogens, the utility of adaptive immunity is to focus on pathogen-specific clearance mechanisms to protect the host from damage and death. By contrast, vaccines aim to prime adaptive immunity to anticipate future pathogens by generating antigen-specific immune memory. Most effective vaccines in use today rely heavily on the long-term protection of high-affinity B cell memory that develops under the antigen-specific guidance of helper T (Th) cells. In this review, we present recent advances to the understanding of Th cells with emphasis on the progressive developmental checkpoints that control antigen-specific Th cell fate and impact memory B cell development after protein vaccination (Figure 1).

At the tissue site of initial exposure, inflammation induces dendritic cell (DC) maturation and migration to local draining lymphoid tissues. In lymph nodes (LN), antigen-experienced DC recruit naïve Th cells expressing T-cell receptors (TCR) with threshold binding for peptide–MHCII complexes (pMHCII) into the adaptive immune response [1]. These early cognate interactions define the first major checkpoint in the development of high-affinity B cell immunity (Figures 1 and 2, Checkpoint I) [2] and are the focus of the first section in this review. Antigen-specific Th cell recruitment and clonal expansion underpin the development of effector Th cell function [3]. In the second section of this review, we present the current thinking and recent information on the development and function of follicular B helper T (T_{FH}) cells and the regulation of B cell responses [4•]. We consider effector T_{FH} cells that regulate pre-GC B cell fate (Figure 1, Checkpoint II) and GC T_{FH} that regulate memory B cell development (Figure 1, Checkpoint III) as separate T_{FH} compartments with separable impact on B cell immunity. Finally, we address the issue of Th cell memory and the regulation of memory B cell responses to antigen re-exposure (Figure 3, Checkpoint IV). There is new evidence for persisting antigen *in vivo* that plays a role in both effector and memory Th cell development. We propose the existence of antigen-specific memory T_{FH} cells and describe what is expected of their function *in vivo*.

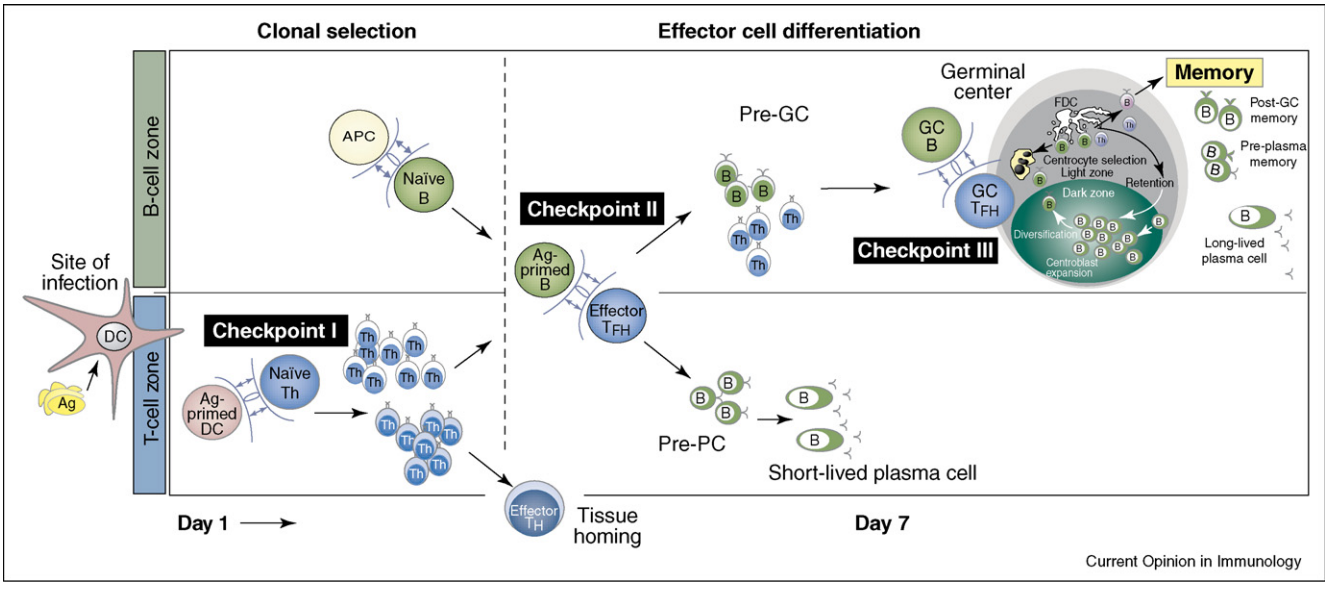
Clonal selection in the Th cell compartment

The recognition of pMHCII complexes by antigen-specific Th cells is the central and defining attribute of antigen-responsive Th cells. Although there are many 'bystander' influences guiding the outcome of adaptive responses, the 'cognate' regulation of cell fate focuses on specific TCR–pMHCII binding. DCs are uniquely efficient at protein antigen uptake, processing and presentation of pMHCII complexes and serve as the initiators of early pMHCII-specific selection events *in vivo*.

DC maturation *in vivo*

Multiple subsets of DCs are available to process and present antigen to the adaptive immune system. Recent studies indicate that LPS-activated DCs enter LNs quite motile, but rapidly coalesce with dense cellular networks of DCs already clustered at the T–B borders of secondary lymphoid tissue [5]. DC subsets can also reside in close association with the reticular conduit network of LNs in order to access foreign antigens rapidly [6]. Local skin inflammation can also induce separate waves of dermal DC (dDC) migration followed by Langerhans cells (LCs) [7]. Importantly, there appear to be separate fibroblastic networks that underpin organization and movement

Figure 1



Helper T cell regulated checkpoints in memory B cell evolution. Protein vaccination induces antigen (Ag) uptake, processing and presentation of pMHCII complexes and local DC maturation and migration to draining secondary lymphoid tissues. In the T cell zones, pMHCII$^+$ DCs make stable contact with naïve pMHCII-specific naïve Th cells to define the first major checkpoint in the development of Th cell regulated B cell immunity (Checkpoint I). Antigen-specific Th clonal expansion and migration of effector T_{FH} cells to the T–B borders result in stable contacts with antigen-primed pMHCII$^+$ B cells at Checkpoint II. Antigen-specific B cells then either progress in an extra-follicular pathway to switch antibody isotype and become short-lived plasma cells (PCs) or enter the germinal center (GC) pathway to memory B cell development. The GC pathway for B cells involves clonal expansion, BCR diversification and antigen-driven selection for high-affinity variants. Antigen-specific contact with GC T_{FH} cells at this developmental juncture defines a critical checkpoint in the survival and export of high affinity GC B cells into the memory B cell compartment (Checkpoint III). Importantly, the unique cellular outcomes at each checkpoint are driven by the quality of TCR–pMHCII interactions and the presence of molecular co-modifiers that differ substantially at each progressive stage of development. Abbreviation: FDC, follicular dendritic cells.

within steady-state LN microenvironments [8••]. The method of antigen delivery also impacts the type of adaptive immunity that develops. Initial targeting of protein antigen to CD8α$^+$ DCs using antibodies to DEC 205 efficiently primes long-lived T cell help for antibody recall responses [9]. However, targeting CD8α$^+$ DCs preferentially induces pMHCI complexes while targeting CD8α$^-$ DCs induces pMHCII complexes [10••]. Antigen-bearing DCs have also been directly implicated in the initial priming of naïve B cells in Th cell dependent immune responses [11•]. Thus, temporal and spatial constraints on DC migratory behavior and the method of antigen priming fundamentally impacts DC maturation *in vivo*. The molecular and cellular context of these pMHCII complexes can then substantially alter antigen-specific Th cell fate at this early juncture of development.

Affinity thresholds regulate Th cell selection

Antigen specificity is the cornerstone of adaptive immunity. However, the rules that drive antigen-specific clonal selection in the T cell compartment remain poorly resolved. Many TCR–pMHC co-complex structures have now been solved to reveal a substantial amount of variability in the diagonal docking of TCR to pMHC [12]. Furthermore, there is no consensus regarding the physical or biochemical attribute of pMHC binding that initiates TCR signal transmission within the T cell. There is evidence for TCR conformational changes upon pMHC binding that are different after strong or weak binding [13]. Comparisons of bound and unbound TCR also indicate an 'induced-fit' level of accommodation in the CDR3 junctional loops of the TCR [14]. Biophysical analyses show a loss of entropy that is also indicative of a flexible binding site. These types of studies suggest that the CDR1/2 of the TCR initially scans the MHC helices and then the CDR3 loops fold over the peptide to achieve a stable state [14]. Surprisingly, pMHCII binding at the surface of antigen presenting cells (APCs) also utilizes endogenous pMHCII complexes to increase the valency of the interactions and drive T cell activation [15••]. Hence, TCR recognition involves conformational cooperativity within single interactions that will then promote polyvalent multimer formation at the cellular interface between T cell and APC.

TCR binding to foreign pMHC complexes are characteristically low affinity interactions (1–50 μM). Nevertheless, most models still favor TCR–pMHC affinity-based