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Review Article

CTL-mediated APC elimination: Constraining effective humoral immunity

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Abstract

Cytotoxic CD8⁺ T lymphocytes (CTLs) are classically viewed as effectors of cellular immunity, eliminating infected or malignant cells. Yet an underappreciated facet of their biology is their capacity to impose negative regulation on antigen-presenting cells (APCs), including dendritic cells (DCs), macrophages, and B cells. In this review, we explore the hypothesis that overly robust CTL responses may inadvertently impair humoral immunity by prematurely trimming APC lifespan, constraining T follicular helper (Tfh) induction, and reducing antibody production and immune durability. We review evidence for CTL-mediated APC killing, mechanistic modulators, and cross-talk with helper T cells, then connect this to Tfh–B cell dynamics, immune complex formation on follicular dendritic cells (FDCs), and long-term antibody retention. We also discuss how this process fits into broader immune regulation, its clinical implications for autoimmune diseases, cancer, and infections (including limited human studies), and propose experimental strategies to validate or disprove this regulatory axis. Finally, we outline implications for vaccine design.

Keywords: Immunity, Immunology, Vaccine, T cells, B cells, Dendritic cell, Antigen-presenting cell, Antibody

Introduction

Effective immunization aims to elicit both robust cellular immunity (often mediated by CD8⁺ cytotoxic T lymphocytes or CTLs) and durable humoral immunity (antibodies plus memory B cells and plasma cells). However, conflicting demands may exist: CTLs actively kill cells presenting cognate antigen, whereas humoral immunity depends on sustained antigen presentation, germinal center (GC) reactions, and immune complex retention. This raises a provocative question: can CTLs, in exerting their effector function, inadvertently undermine humoral immunity?

Here, we assess a multi-step model in which excessive CTL activity shortens the lifespan of antigen-loaded DCs, thereby constraining Tfh priming and B cell help, reducing peak antibody titers, and diminishing immune durability via lower immune-complex deposition on FDCs. We review mechanistic evidence, integrate this into immune regulation, discuss clinical implications, and propose experimental paths to test this model and its implications for vaccine development.

Summary of key hypothesis

CTLs eliminate APCs to prevent immune overactivation, but this can limit humoral responses by reducing Tfh support and FDC antigen retention.

CTL-mediated Killing of APCs: Evidence, Mechanism, and Regulation

Empirical evidence for CTL elimination of APCs

In a landmark *in vivo* mouse study, Belz and colleagues showed that antigen-loaded DCs are eliminated in a perforin-dependent manner by CTLs, and that in perforin-deficient mice, antigen-specific CD8⁺ T cells expand further upon repeated DC immunizations (i.e., without

the "gatekeeping" DC loss) [1–4]. That study also localized DC elimination to peripheral tissues, not within draining lymph nodes, suggesting spatial restriction of CTL–DC killing [1–5].

In DC-based cancer vaccination settings, CTL presence has been observed to suppress the boosting of CTL responses—interpreted as CTLs eliminating the booster DCs before they can further prime [3]. *In vitro* human studies show that effector $CD8^+$ T cells can kill immature DCs in a granzyme B– and perforin–dependent manner, and inhibitors of granzyme B reduce DC death [1–6]. Human DCs express PI-9 (a granzyme B inhibitor), which provides partial resistance to CTL killing, but this can be overcome at high effector:target ratios [7,8]. For instance, *in vitro* assays with human monocyte-derived DCs demonstrate that CD40L or LPS activation induces PI-9 expression, conferring resistance, though prolonged exposure leads to eventual apoptosis [6,7]. Limited human *in vivo* evidence comes from genetic disorders: perforin defects in Familial Hemophagocytic Lymphohistiocytosis (FHL) lead to $CD8^+$ T cell accumulation, potentially due to impaired DC elimination [6]. Similarly, in Autoimmune Lymphoproliferative Syndrome (ALPS), loss of DC sensitivity to TRAIL-induced death (a CTL-related pathway) is observed, suggesting dysregulated DC survival contributes to lymphoproliferation [6].

In addition to DCs, other APCs, such as macrophages [9–13] and B cells [14–17], can also be killed by corresponding CTLs. It was demonstrated in some studies that cytotoxic T lymphocytes (CTLs) can kill macrophages functioning as APCs. This process is typically MHC class I-restricted and antigen-specific, contributing to immune regulation (e.g., eliminating infected or overactivated macrophages) or pathology (e.g., in viral infections or autoimmunity). Potula *et al.* [10] used human monocyte-derived macrophages pulsed with HIV peptides, co-cultured with HIV-specific CTLs, and measured lysis via flow cytometry and viral clearance assays. This study shows that HIV-1 infection upregulates indoleamine 2,3-dioxygenase (IDO) in brain macrophages, rendering them resistant to antigen-specific CTL lysis. Pharmacologic IDO inhibition restored CTL killing, confirming macrophages as APC targets in a viral context. Münz *et al.* [11] demonstrated that $CD8^+$ CTLs lyse *Toxoplasma gondii*-infected macrophages presenting pathogen-derived peptides on MHC class I by *in vitro* and *in vivo* (mouse models) assays, which showed perforin/granzyme-dependent killing, highlighting CTLs' role in eliminating APCs harboring persistent vesicular pathogens. Studies with cancer models also exhibited CTLs mediated killing to macrophages [12–14]. Multiple studies have demonstrated that B cells, when they are professional APCs, are susceptible to CTL killing. This process also involves MHC class I-restricted recognition of antigen presented by the B cell, leading to CTL-mediated lysis via mechanisms such as perforin/granzyme exocytosis or Fas/FasL interactions (like DCs and macrophages) [15–18]. A pivotal study [15] showed that antigen-bearing B cells, acting as APCs, are specifically lysed by activated $CD8^+$ T cells (OT-I CTLs) upon antigen recognition. This lysis occurs through TCR engagement with MHC class I-presented antigen, resulting in B cell death and subsequent tolerance in the responding CTLs [15,16]. In another study [17], BAFF-activated human B cells, pulsed with HIV-1 peptides as APCs, educated antigen-specific CTLs that subsequently lysed HIV-1-infected $CD4^+$ T cells. The study explicitly notes that these B cells, enhanced for antigen presentation via MHC I/II upregulation, become targets for the generated CTLs, demonstrating efficient lysis in *ex vivo* assays. This highlights B cells' dual role: priming CTLs while being vulnerable to them post-activation. In a model using bispecific CD19xCD3 antibodies [18], T cells (recruited as CTLs) lysed allogeneic and autologous B cells presenting CD19 antigen. Lysis was perforin-dependent but Fas-independent, confirming MHC-independent yet antigen-directed killing. This mimics natural antigen presentation scenarios where B cells display surface antigens for CTL recognition. In a study with SCID mouse models for cancer therapy [19], antibody-targeted HLA class I/II complexes on B cells (as APCs) induced CTL expansion and subsequent lysis of coated B cell targets *in vivo*. In this study, anti-viral CTLs lysed B cells presenting tumor antigens, supporting B cell vulnerability during antigen-specific interactions. In a study of Blanchard *et al.* [20], B cells presenting staphylococcal enterotoxin A (SEA) as APCs were lysed by CTLs via ATP release during antigen presentation, leading to necrosis rather than apoptosis. This downregulates immune responses by eliminating APCs, with IFN-γ-activated B cells showing heightened sensitivity. Thus, the capacity for CTLs to eliminate APCs is well supported in a variety of experimental systems, particularly under conditions of high CTL numbers and APC antigen burden.

While most direct evidence stems from animal models, human *in vitro* and *ex vivo* studies (e.g., with HIV-pulsed macrophages and B cells) corroborate CTL-mediated APC killing, though *in vivo* human data remain indirect and limited by ethical constraints.

Key summary: CTL killing of APCs is antigen-specific and perforin/granzyme-dependent, observed across DCs, macrophages, and B cells in both animal and human systems.

Mechanistic basis and modulating factors

The primary cytotoxic machinery used is perforin + granzyme B and/or Fas/FasL interactions, consistent with classic CTL-mediated apoptosis [4-6,15–18]. The functional susceptibility of APCs depends on antigen presenting state. In our studies with macrophages, the concentration of antigens used to sensitize the target macrophages is positively correlated to the lysis of the target cells [9], suggesting CTL-mediated APC killing is also related to the strength of antigen presented by APCs. Although mature or "licensed" DCs were reported to resist CTL lysis more than immature DCs via CD40 ligation, PLS, or TLR stimuli [4,6,7], CTL-mediated DC killing was not abolished, especially significant DC lysis can be observed at higher effector:target ratio. Moreover, studies using mice have shown that antigen-loaded DCs are eliminated by specific $CD8^+$ T cells and fail to accumulate in the draining lymph node. Researchers have observed this process directly by tracking fluorescently labeled DCs. Only the specific, antigen-loaded DCs were cleared, while other DCs remained unaffected [21]. Studies on viral infection also exhibited that the lifespan of mature DCs could be shortened by the activated CTLs [22–24]. There is a choreography of phases: early in the response, CTLs may be more aggressive toward DCs, but as memory sets in, CTLs (or memory CD8s) may transition into a helper-like role, prolonging DC survival and promoting further immunity [6,25]. $CD4^+$ helper T cells also contribute to DC protection: CD40L–CD40 interactions can induce DC expression of anti-apoptotic regulators, such as SPI-6/PI-9 family, and reduce CTL-mediated DC death [7,8]. In an *in vivo* study of herpes simplex virus (HSV) infection shows that in the presence of CTLs, transferred DCs may be eliminated from draining lymph nodes, but co-transfer of virus-specific $CD4^+$ T cells prolongs antigen presentation by prolonging DC survival [26]. However, these longer survived DCs would be also eliminated by more robust CTLs they stimulated [22–24].

These findings suggest that APC fate can be determined by CTL aggression, although it is also affected by helper T cell signals and DC maturation state. Mature dendritic cells acquire transient resistance to cytotoxic T-lymphocyte–mediated killing through upregulation of anti-apoptotic and cytoprotective pathways. However, this resistance is relative rather than absolute. When the effector CTL pool expands and their cytolytic activity intensifies, these defenses are overcome, leading to elimination of antigen-bearing DCs. This dynamic equilibrium allows sufficient priming but prevents prolonged antigen presentation and immune overactivation.

Key summary: Mechanisms involve perforin/granzyme and Fas/FasL; modulators include APC maturation, antigen dose, and $CD4^+$ help, balancing killing with protection.

Quantitative/ Kinetic considerations

At low CTL densities, killing may follow a linear or quasi–mass-action model; at high CTL densities, saturation or target scarcity may limit further killing. Some mathematical immune models reflect such saturation dynamics [25]. The lifespan baselines of different APCs vary, but all are finite. When these cells function as APCs, antigen processing and presentation often shorten their lifespan. A typical example is that mature DCs have limited half-lives (days to a few weeks, depending on context). Thus, CTL killing may truncate the tail-part of antigen presentation performed by mature DCs [8]. Such a curtailment of APC lifespan could play a critical role in the weakened stimulation of Tfh cells and further in lower MHC class II immune responses and antibody production. Spatial compartmentalization is critical as CTLs may more readily access DCs in peripheral tissues or interstitial compartments, but less so in tightly controlled lymph node microenvironments [2,26]. Temporal delay of DC elimination should be considered. Naive $CD8^+$ T cells do not immediately become cytolytic; it takes time for differentiation, expansion, and trafficking [27]. During that window, DCs may have already engaged in T cell priming [28], further activating CTLs and Tfh cells, which depends on antigen protein structure. If CTLs were dominantly activated, the DCs would be eradicated faster, and thereby the DCs have less chance to keep activating Tfh cells for enhancing and maintaining MHC class II immune responses, resulting in impaired humoral immunity. Thus, the suppressive effect of CTLs on APCs could be modulated by kinetic lags, spatial constraints, and regulatory feedback that may blunt or delay killing, but the outcome could still be the reduction of antibody production and immune durability.

Key summary: Killing kinetics are influenced by CTL density, APC lifespan, and spatial/temporal factors, potentially truncating Tfh priming.

Integration into broader immune regulation and significance

CTL-mediated APC elimination serves as a regulatory checkpoint to prevent immune overactivation. By limiting APC lifespan, it curbs excessive $CD8^+$ T cell expansion (as seen in perforin-deficient models) and downregulates antigen presentation once threats are cleared, promoting homeostasis [1–5,25]. This "gatekeeping" role is significant in balancing cellular and humoral arms: it prevents CTL dominance from overshadowing antibody responses, but excessive killing can tip the scale toward humoral impairment. In evolutionary terms, this may favor rapid clearance of acute threats while constraining long-term humoral memory in variable pathogens like influenza.

From Dc Trimming to Compromised Humoral Immunity: Tfh, B Cells, and Immune Complexes

Role of DCs in Tfh induction and B cell help

Conventional DCs (cDCs) are indispensable for priming naive $CD4^+$ T cells and guiding their differentiation toward Tfh lineage [29,30]. DCs present antigen via MHC class II, supply costimulation (e.g., ICOSL, CD80/86), and secrete cytokines like IL-6 or IL-12 to influence helper subset decisions [29]. Early Tfh "programming" typically occurs in the T cell zone before migration of Tfh precursors to the B cell follicle, where they engage germinal center B cells [30]. A truncated DC antigen-presentation window (due to CTL elimination) could reduce the size and quality of the emerging Tfh pool, thereby limiting B cell help, germinal center seeding, and plasmablast differentiation [27,29,30].

Key summary: DCs drive Tfh differentiation; CTL shortening this limits B cell support.

Consequences for antibody responses

Due to APC lifespan being shortened, a smaller or less functional Tfh pool reduces B cell activation, germinal center magnitude, somatic hypermutation, and selection, ultimately diminishing plasma cell output and antibody titers. Empirical vaccine models confirm the correlation between Tfh magnitude and antibody peak [27,30,31].

Humoral immune durability relies on the activities of follicular dendritic cells (FDCs). In secondary lymphoid follicles, FDCs retain antigen in the form of immune complexes (ICs). These ICs are captured via complement receptors (CR1/CR2), Fc receptors, or other binding interactions, and can persist for extended periods [28]. Persistent antigen display on FDCs provides "antigen memory" to germinal center B cells, enabling continuous rounds of selection and maturation even as plasma cell output evolves [28,31]. Lower antibody levels (resulting from reduced B cell help) imply fewer antigen–antibody complexes, hence lower IC density on FDCs. Less antigen retention accelerates germinal center contraction, reduces affinity maturation, and weakens memory B cell and long-lived plasma cell generation [31,32]. In vaccine settings with limited antigen persistence, the robustness of FDC antigen retention is often a rate-limiting determinant of long-term humoral durability — thus any upstream reduction in IC formation could accelerate waning immunity [32,33].

Key summary: Reduced Tfh leads to lower antibody titers and FDC ICs, impairing magnitude and durability.

Mechanistic summary

Since CTLs recognizing antigenic peptides on APCs kill APCs (via induction of apoptosis), the shortened APC lifespan restricts the window of antigen presentation to $CD4^+$ T cells (especially Tfh precursors). Fewer or lower-quality Tfh cells reduce B cell help, germinal center seeding, and plasma cell differentiation—resulting in a lower peak antibody titer. The reduced antibody output limits antigen–antibody complex formation, meaning fewer immune complexes on FDCs. Lower IC density accelerates GC contraction, limits affinity maturation, and diminishes long-term memory/plasma cell maintenance—leading to reduced durability of humoral immunity. Consequently, excessive CTL responses can suppress both magnitude and durability of antibody responses.

In addition, Tfh cells play a central role in sustaining germinal center (GC) reactions and promoting long-term antibody production by shaping the function of follicular dendritic cells (FDCs) through cytokine-mediated signaling. Among Tfh-derived cytokines, interleukin-21 (IL-21) is particularly critical. It acts both autocrinally to stabilize Tfh function and paracrinally to enhance B cell maturation, class-switch recombination, and plasma cell differentiation via STAT3- and Bcl-6–dependent transcriptional programs. Importantly, FDCs express IL-21 receptors and respond to IL-21, as well as to other Tfh-associated cytokines such as IFN-γ and TNF. IL-21 signaling through the JAK1/3–STAT3 pathway upregulates the expression of complement receptors CR1 (CD35) and CR2 (CD21), as well as the low-affinity Fc receptor FcγRIIb on FDCs. This cytokine-driven modulation increases the capacity of FDCs to capture, retain, and recycle immune complexes (ICs) on their dendritic surfaces, preserving the structural integrity of conformational epitopes and facilitating continuous B cell receptor (BCR) engagement. Persistent BCR signaling allows GC B cells to survive and maintain antigen presentation to Tfh cells, which in turn reinforces IL-21 secretion and perpetuates a positive feedback loop among Tfh cells, FDCs, and GC B cells. Through this dynamic circuit, IL-21–dependent enhancement of immune complex density on FDCs supports prolonged GC reactions, greater affinity maturation, expanded pools of long-lived plasma cells, and ultimately more durable humoral immunity [28,34,35]. Therefore, weakened Tfh responses caused by shortened APC lifespan can also directly reduce the immune complex deposition on FDCs and further diminish the durability of the antibody responses.

Implications for Infection Immunity, Vaccine Design, and Clinical Applications

Some virus infections and their corresponding vaccines can induce durable protective immunity, but others not. Smallpox, measles, mumps, and many others can generate lifetime immunity post-infection, and the immunity induced by their vaccines can last many years. In contrast, influenza, COVID, RSV infection can only induce several months' to at most two years' protective immunity [36–40]. Interestingly, all the pathogens that do not elicit permanent protective immunity can induce long-term even lifetime cellular immunity, including CTL responses. This indicates that cellular immunity only has limited contribution to the durability of immunity, compared to humoral immunity [40–43]. Moreover, the term of effective immunity always depends on the level of protective antibodies [44–46]. Therefore, in order to acquire durable immunity, any factors that can potentially negatively affect humoral immunity in vaccine design should be avoided [47–50].

Vaccine Design

Main factors that affect humoral immunity, from antigen itself, are epitopes that interact with B cells, Tfh cells, and CTLs. The epitopes that bind to B cells can induce antibody production, and it is a critical part of humoral immunity. The epitopes presented by APCs to Tfh cells can stimulate Tfh cells to enhance and maintain the antibody production function of B cells, through MHC class II pathway. Only CTLs may have negative effects on antibody production by killing APCs. Moreover, many adverse effects of vaccines are related to cellular immune responses enhanced by vaccines [51–53]. In order to mitigate CTL interference with magnitude and durability of antibodies elicited by vaccines, several strategies should be considered in vaccine design:

1. **Modification of antigen epitopes [53–55]:** Reduce CTL epitopes or reduce the affinity of epitopes to CTLs and increase the affinity of epitopes to the Tfh cells by modifying the amino acid sequence. This needs to consider the effects of HLA types in humans.
2. **Temporal separation [33,56]:** Sequence immunization so that APC–Tfh interactions proceed before strong CTL activation (e.g., prime with T helper–biased adjuvant, boost later with CTL-focused vector).
3. **APC protection mechanisms [6,7]:** Engineer vaccine APCs or antigen-presenting vehicles to express granzyme inhibitors (PI-9 / SPI-6) or anti-apoptotic factors.
4. **Moderated CTL induction [33,57]:** While CTL responses are desirable, calibrating their magnitude (rather than maximum possible) might avoid suppressing humoral outcomes.
5. **Antigen scaffolding/immune complex optimization [32]:** Design antigens that promote stable immune complex formation (e.g., via Fc fusion, complement-binding tags), so that even modest antibody titers yield efficient FDC deposition.
6. **Adjuvants or signals favoring APC survival [8,32]:** Include factors (e.g., CD40 agonists, survival cytokines) to prolong antigen presentation windows.

Clinical Implications

This hypothesis has broader clinical relevance beyond vaccines. In **infections**, CTL-mediated APC elimination may explain waning humoral immunity in chronic or variable pathogens like HIV, where IDO upregulation in macrophages confers resistance but overall limits antibody durability [10,39,40]. In acute viral infections, it prevents overactivation but may hinder responses to variants ("original antigenic sin") [6].

In **cancer**, DC-based therapies often fail due to CTL killing of injected DCs, suppressing boosting and antitumor immunity [3,21]. Enhancing APC resistance (e.g., via PI-9) could improve outcomes, though human data are limited to *in vitro* studies [6,7].

In **autoimmune diseases**, dysregulated APC killing may contribute to pathology: impaired elimination (e.g., in FHL or ALPS) leads to prolonged autoantigen presentation, T cell accumulation, and autoantibody overproduction [6]. Conversely, excessive killing might protect by limiting autoantibody, suggesting therapeutic modulation of CTL-APC interactions.

While animal models predominate, human genetic syndromes and *in vitro* assays provide indirect support, highlighting the need for translational studies.

Experimental Validation Roadmap

1. **Perforin-knockout vs wild-type immunization [1,3]**: Use matched vaccine antigens and compare antibody peak levels and durability in perforin-deficient vs control animals, particularly where CTL induction is strong.
2. **Temporal CTL blockade [58]**: Administer anti-CD8 or cytotoxic inhibitors transiently after immunization and measure effects on Tfh numbers, antibody titers/duration, and GC dynamics.

3. ***In situ* DC survival tracking [2,59]**: Label antigen-bearing DCs (e.g. fluorescent or barcoded) and monitor survival post-immunization in the presence or absence of CTL responses; correlate with Tfh induction kinetics.
4. **Manipulation of PI-9/survival pathways [6,7]**: Engineer DCs used in vaccines to overexpress PI-9 or anti-apoptotic molecules, and test whether that protects them from CTL killing and enhances humoral outcomes.
5. **Quantify FDC immune-complex density [28,31,32]**: In different CTL vs control conditions, measure antigen–antibody complex density on FDCs and correlate with GC maintenance and memory B cell/plasma cell numbers.

Summary and Concluding Remarks

This review offers a refined, testable hypothesis: that excessive $CD8^+$ CTL activity may act as a brake on humoral immunity by eliminating APCs, thereby restricting Tfh help and downstream B cell responses, ultimately reducing both antibody magnitude and durability via weakened immune-complex formation on FDCs.

While key links in this chain are supported, especially by CTL-mediated APC killing and CTL suppression of APC-based vaccines, the improvement of antibody magnitude and durability by adjusting CTL activities remain speculative and worthy of empirical validation.

For vaccine development, this model suggests that immunization regimens aiming for humoral immunity may benefit from tuning CTL strength, timing, and APC protection, rather than maximizing CTL induction indiscriminately [33,56,60].

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