Cathepsin S Regulates Class II MHC Processing in Human CD4+ HLA-DR+ T Cells

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Cathepsin S Regulates Class II MHC Processing in Human CD4⁺ HLA-DR⁺ T Cells

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Although it has long been known that human CD4⁺ T cells can express functional class II MHC molecules, the role of lysosomal proteases in the T cell class II MHC processing and presentation pathway is unknown. Using CD4⁺ T cell clones that constitutively express class II MHC, we determined that cathepsin S is necessary for invariant chain proteolysis in T cells. CD4⁺HLA-DR⁺ T cells down-regulated cathepsin S expression and activity 18 h after activation, thereby ceasing nascent class II MHC product formation. This blockade resulted in the loss of the invariant chain fragment CLIP from the cell surface, suggesting that—like professional APC—CD4⁺ HLA-DR⁺ cells modulate self-Ag presentation as a consequence of activation. Furthermore, cathepsin S expression and activity, and concordantly cell surface CLIP expression, was reduced in HLA-DR⁺ CD4⁺ T cells as compared with B cells both in vitro and ex vivo. The Journal of Immunology, 2009, 183: 0000 – 0000.

CD4⁺ T cells are activated by TCR engagement of peptide/class II MHC complexes on APCs to initiate an adaptive immune response, but can themselves also express class II MHC (1, 2). The expression of class II MHC on CD4⁺ T cells occurs in most mammalian species (3), the exception being mice, which do not transcribe the CIITA promoter III in CD4⁺ T cells (4, 5).

In the human system, expression of HLA-DR, the most prevalent class II MHC molecule, was first described as a marker of activated T cells (2). Patients with chronic autoimmune disease, inflammation, and the recent recipients of immunizations exhibited a higher frequency of HLA-DR⁺ T cells in the peripheral blood as compared with healthy donors (6). Yet, for human CD4⁺ T cells, HLA-DR is more than a biomarker of activation. Class II MHC on these cells is functional and can be used to present peptide Ag to activate responder CD4⁺ T cells in vitro (7–9). Furthermore, recent studies have identified HLA-DR expression on CD4⁺ T cells in the blood of healthy donors, specifically a subset of CD4⁺CD25high Fox3⁺ natural regulatory T cells, and suggest that HLA-DR may have a functional role in these cells (10).

Although the class II MHC processing and presentation pathway has been studied extensively in professional APC, this pathway in human CD4⁺ T cells has not been characterized. This is not a trivial issue, as many of the enzymes involved in the generation of peptide epitopes are not ubiquitously expressed. HLA-DR maturation is regulated by the invariant chain (Ii),3 which acts as a surrogate substrate and trafficking chaperone (11). As the MHC:Ii complex migrates through the endo/lysosomal compartment, resident proteases systematically degrade the this chaperone, leaving only the Ii fragment CLIP to occlude the class II MHC binding pocket. These same proteases hydrolyze self and foreign proteins to generate peptide epitopes, which ultimately displace CLIP and are loaded into the class II MHC binding pocket with the aid of the loading molecule HLA-DM (12).

Key proteolytic regulators of class II MHC processing have been identified in professional APC with the use of knock-out mice and specific protease inhibitors (13, 14). Blockade of Ii degradation results in the accumulation of Ii intermediates and can lead to a corresponding decrease in surface expression of class II MHC products (15, 16). In human B cell lines, treatment with the cysteine protease inhibitor leupeptin or the cathepsin S inhibitor leucine-homophenylalanine-vinyl sulfone (LHVS) blocks successful degradation of Ii (17). Characterization of cathepsin S (CatS) knock-out mice has further implicated CatS in the terminal cleavage of Ii to yield CLIP in professional APC (13). Further studies, however, have demonstrated a cell type-specific role for cysteine proteases in these later stages of Ii processing. Catl in thymic epithelial cells and CatF in macrophages can also perform this cleavage (18) (19).

Although B and T cells are derived from a common precursor, these cells ultimately differentiate into functionally unique lineages with distinct trafficking pathways, organization, and composition within their intracellular processing compartments. This prompted us to explore in detail the biosynthesis of human class II MHC products in MHC-identical B and T cells. In this study, we demonstrate, using CD4⁺ T cell clones, that CatS is a key enzyme required for proteolysis of Ii in CD4⁺ HLA-DR⁺ T cells. We find that activation-induced regulation of CatS expression and activity leads to the down-regulation of CLIP expression in CD4⁺ HLA-DR⁺ T cells both in vitro and ex vivo. Our data indicates that CD4⁺ HLA-DR⁺ T cells modulate peptide epitope presentation postactivation, and furthermore suggests that presentation of non-CLIP self-peptide may be integral to the function of class II MHC on these cells.

Materials and Methods

Cell culture reagents and Abs

Cells were cultured in RPMI 1640 medium supplemented with 2 mM l-glutamine, 5 mM HEPES, 100 U/ml penicillin/streptomycin (all from

1Abbreviations used in this paper: Ii, invariant chain; LHVS, leucine-homophenylalanine-vinyl sulfone; Cat, cathepsin; AEP, asparagine endopeptidase; EBV, Epstein-Barr Virus.

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BioWhittaker), 0.5 mM sodium pyruvate, 0.5 mM nonessential amino acids (from Life Technologies) in 96-well U-bottom plates or 25 cm² vented flasks (CoStar). T cell clone medium additionally received 5% human AB serum (Meditech) and 25 U/ml recombinant human IL-2 (Tecin, National Cancer Institute). The medium for the Epstein-Barr Virus (EBV)-transformed B cell lines was supplemented with 8% FBS. The αCD3 (UCHT1 and H13a), αCD4 (RPA-T4), αCD8 (CD28.2 and 3D10), αCLIP/HLA-DR (C15/L), αHLA-DR (L243 and Tu 36), α class II HMC (Tu39), α HLA-DM (Ma2D1M), and αCD19 (1D3) Abs were purchased from BD Pharmingen.

Cell isolation
Whole mononuclear cells were isolated from healthy individuals after informed consent in green-capped, heparinized tubes by Ficoll-Hypaque (GE Healthcare) centrifugation. CD19⁺ B cells were isolated using CD19 microbeads (Miltenyi Biotec). Total CD4⁺ T cells were isolated via the CD4⁺ T cell negative isolation kit II (Miltenyi Biotec) and incubated with an excess volume of fluorochrome-labeled Abs against HLA-DR (L243 PerCP), CD26 (Dreg 56 APC), CD122 (Dreg 69 FITC), CD3 (UCHT1) and activated T cell clones, required for donor-to-donor variability in protein expression, enzyme activity, and MHC haplotype.

Results
Establishment of CD4⁺ HLA-DR⁺ T cell clones
Class II MHC is a traditional biomarker of activated human CD4⁺ T cells (2), but relatively little is known about endogenous class II expression, processing, and Ag presentation in these adaptive, non-professional APC. To assess class II MHC expression in CD4⁺ T cells at the single cell level, we generated CD4⁺ T cell clones from the peripheral blood of healthy donors. We propagated these clones in APC-free cultures to ensure that our analysis was restricted to endogenous class II MHC expression and would exclude acquisition of class II from traditional APC. We compared class II MHC synthesis in these clones to genetically identical EBV-transformed B cell lines. This comparison allowed us to control for donor-to-donor variability in protein expression, enzyme activity, and MHC haplotype.

Consistent with previous reports (24, 25), chronically activated CD4⁺ T cell clones acquired constitutive cell surface expression of the class II MHC determinants HLA-DR, HLA-DP, and HLA-DQ (Fig. 1, A and B, data not shown). This basal level of class II expression was up-regulated by polyclonal activation of T cell clones with αCD3 and αCD28 (Fig. 1). After 5 days of activation, these clones expressed cell surface class II MHC equivalent to that of EBV-transformed B cells. Additionally, activated CD4⁺ T cell clones up-regulated CITTA and HLA-DRα mRNA after treatment with αCD3 and αCD28 (Fig. 1, D and E), in tandem with cell surface protein expression. We confirmed that expression of class II MHC was endogenous by metabolic labeling with [³⁵S]-methionine, followed by immunoprecipitation of HLA-DR in resting and activated T cell clones (Fig. 1F). Synthesis of HLA-DRα and β-chains, as well as α iaporphins p41 and p31, was up-regulated at 3 and 5 days postaccloration in these cells, although SDS-stable dimer formation was not observed for all individuals assayed. These results indicate that human CD4⁺ T cell clones synthesize and express class II MHC, corroborating previous reports of HLA-DR expression by CD4⁺ T cell clones (7, 9).

Class II MHC processing in CD4⁺ T cell clones requires cysteine proteases
We detected the i fragment CLIP on the surface of CD4⁺ T cell clones (Fig. 1C) and i isoforms bound to HLA-DR complexes immunoprecipitated from [³⁵S]-methionine-labeled cells (Fig. 1F). Given these findings, we hypothesized that CD4⁺ T cell clones, like professional APC, use the endosomal class II MHC processing pathway. In this pathway, HLA-DR α- and β-chains are assembled on the i chaperone, which must be processively cleaved by resident proteases in the endo-lysosomal compartment to allow peptide loading.

To identify a proteolytic requirement for class II MHC αβ dimer formation in CD4⁺ T cell clones, we treated these cells with the pan-cysteine protease inhibitor leupeptin or the pan-aspartyl protease inhibitor pepstatin, pulsed the treated cells for 45 min with [³⁵S]-methionine to label nascent proteins, and then chased the radiolabeled proteins for up to 3 h before immunoprecipitation of HLA-DR complexes and associated i fragments. In EBV-transformed B cells, treatment with leupeptin but not pepstatin inhibited i cleavage; blockade of cysteine proteases in these cells generated a 22 kDa peptide (the p22 leupeptin induced peptide) and prevented successful SDS-stable dimer formation (αβ-peptide) (16) (Fig. 2A). Likewise, leupeptin treatment, but not pepstatin treatment, inhibited HLA-DR maturation in a donor-matched CD4⁺ T cell clone (Fig. 2B). After 2 h of chase, the i fragments p22 and p24 could be resolved in T cell clones treated with leupeptin alone but not in those treated with pepstatin. Leupeptin treatment also
disrupted SDS-stable dimer formation in T cell clones. These findings indicate that cysteine protease activity is required for successful class II MHC processing in both B and CD4⁺ T cells.

Although we found cysteine protease activity necessary for class II MHC maturation in both B and T cells, other proteases can cleave Ii and alter the kinetics of class II processing. We observed in some clones the formation of p24 upon leupeptin treatment and reduced formation of p22 with upon treatment with both leupeptin and pepstatin (Fig. 2, B and C), phenomena that were not observed in donor-matched BCL. Cysteine proteases may dominate class II processing in both B and T cells, but our data argues for differences in the proteolytic repertoire between these two cellular subsets that could subtly alter class II processing.

AEP does not contribute to Ii processing in CD4⁺ T cell clones

We have previously reported that asparagine endopeptidase inhibition results in development of p24 in leupeptin-treated BCL and loss of p22 in BCL treated with both leupeptin and pepstatin (21). As we observed similar Ii cleavage fragment patterns in CD4⁺ T cell clones treated with leupeptin and leupeptin/pepstatin (Fig. 3 A), we hypothesized that these cells lack AEP activity. Indeed, AEP mRNA was barely detectable in CD4⁺ T cell clones, as compared with donor matched BCL, or in CD19⁺ and CD4⁺/HLA-DR⁺ T cells ex vivo (Fig. 3A). Furthermore, we could not detect AEP activity in CD4⁺ T cell clones by direct enzymatic assay (Fig. 3B). These findings show that AEP is not significantly expressed in CD4⁺ T cells and therefore does not play a role in class II MHC processing and Ag presentation in these cells.

Cathepsin S inhibition blocks Ii cleavage in CD4⁺ T cell clones

CatS plays a critical role in class II MHC processing in murine and human B cells, dendritic cells, and macrophages (17, 26, 27).
Given the blockade in invariant chain proteolysis imposed by cysteine protease inhibition in CD4⁺ T cell clones (Fig. 2B), we hypothesized that CatS activity is required for processing of class II MHC in these nontraditional APC.

To test this hypothesis, we measured Ii processing and SDS-stable dimer formation in CD4⁺ T cell clones treated either control amounts of DMSO, leupeptin, or 5 nM LHVS (Fig. 4). We used this low concentration of LHVS to selectively inhibit CatS (17, 28, 29). We pulsed inhibitor-treated T cell clones with [35S]-methionine and then chased the radiolabeled proteins for 6 h with unlabeled medium. After chase, we immunoprecipitated properly folded HLA-DR αβ and Ii complexes from these lysates and resolved both Ii cleavage fragments and SDS-stable dimer formation with SDS-PAGE. As observed previously, treatment with leupeptin resulted in blockade of invariant chain degradation and the formation of the fragments lip22 and lip24 (Fig. 4, A and B). Leupeptin furthermore significantly reduced the total percentage of SDS-stable dimer formation (to 26.3 ± 8.02%; mean ± SD; n = 4) (Fig. 4C), confirming a requisite role for cysteine proteases in class II MHC maturation in T cell clones.

Similar to treatment with leupeptin, selective inhibition of CatS successfully impaired HLA-DR maturation in both CD4⁺ T cells and BCL (Fig. 4, data not shown). This treatment resulted in both invariant chain cleavage fragment generation and the reduction of SDS-stable dimers (to 27.5 ± 12.4% SDS-stable dimer formation; mean ± SD; n = 4) (Fig. 4C). Given the impact of 5 nM LHVS treatment on nascent αβ-peptide formation, we conclude that CatS is required for successful Ii cleavage in CD4⁺ T cells.

**Cathepsin S is down-regulated in activated CD4⁺ T cell clones**

Dendritic, B, and γδ⁺ T cells modulate class II MHC processing and presentation early postactivation (30, 31). To determine the effect of short-term activation on class II MHC expression in CD4⁺ T cells, we stimulated T cell clones with PMA and ionomycin or αCD3 and αCD28 for 18 h and then stained for cell surface HLA-DR (Fig. 5A). At this early timepoint, activated CD4⁺ T cells expressed less HLA-DR than resting clones (down to 34.7 ± 1.0% from 54.7 ± 1.6%; p < 0.0001; mean ± SEM; n = 35 clones). These findings are consistent with studies showing that PMA treatment of previously activated, and therefore class II MHC⁺, T cells reduces class II MHC expression on these cells (32).

The loss of HLA-DR from the cell surface coincides with the reduction of both CatS expression and activity, which were significantly decreased in T cell clones after 18 h of activation (Fig. 5, C and D). Down-regulation of cysteine protease expression and activity was restricted to CatS, as CatB and, to a lesser extent, CatL were up-regulated post activation in both clones and HLA-DR⁺ CD4⁺ T cells ex vivo (data not shown). As CatS is required for the optimal formation of nascent HLA-DR complexes (Fig. 4), down-regulation of this protease could account for the reduction of cell surface class II MHC postactivation. Such a direct relationship would imply that CatS actively maintains class II MHC on the cell surface or indicate that T cells rapidly internalize and degrade class II molecules.

To determine the consequence of CatS ablation on HLA-DR expression, we treated CD4⁺ T cell clones for 18 h with leupeptin or LHVS and stained for cell surface HLA-DR. Treatment of CD4⁺ T cell clones with either leupeptin or LHVS was insufficient to reduce the percentage of HLA-DR⁺ cells in the clones tested (Fig. 5, E–G). The mean density of HLA-DR molecules was reduced in some clones after treatment. Significant down-regulation of intracellular HLA-DR was observed only in clones treated with leupeptin (from 88.06 ± 15.92 to 60.48 ± 11.3; mean ± SEM; n = 12; p = 0.0365), but not LHVS (65.78 ± 15.6 and 74.48 ± 18.59), and down-regulation of extracellular HLA-DR expression was not statistically significant (from 20.42 ± 5.97 to 13.8 ± 3.22; mean ± SEM; n = 12; p = 0.0576) (Fig. 5H). Therefore, short-term cysteine protease inhibition did not directly reduce cell surface HLA-DR expression. Of course, continued inhibition of CatS contributes to loss of class II MHC over time because nascent complex formation is blocked (data not shown), but our data indicates that this mechanism cannot by itself account for the observed loss of HLA-DR early postactivation. These results are consistent with the extended half-life of class II MHC molecules (33) and do not provide evidence for rapid turnover of class II in T cells.
Although short-term cysteine protease blockade did not significantly reduce cell surface HLA-DR expression, LHVS treatment did result in the loss of the invariant chain fragment CLIP from the cell surface (Fig. 5, E, G, and H). Indeed, inhibition of CatS alone with 5 nM LHVS reduced expression of CLIP in the HLA-DR binding pocket (from 21.6 ± 0.6% to 10.2 ± 0.4%; p = 0.0007; mean ± SD; n = 32 clones) (Fig. 5G). Continued treatment with LHVS for 48 h also resulted in significant down-regulation of CLIP (34.7 ± 1.9% control to 7.2 ± 0.5% 5 nM LHVS; p = 0.0005; mean ± SEM; n = 12 clones, data not shown), without concomitant loss of total cell surface HLA-DR. As cell surface CLIP was also down-regulated early postactivation, even in individual clones with limited total HLA-DR down-regulation (Fig. 5B), CatS likely plays a role in the maintenance of CLIP on the cell surface.

CLIP fragments bound in the peptide-binding groove of class II MHC heterodimers are exchanged for antigenic peptide through the action of the loading molecule HLA-DM (12), although CLIP exchange can also occur in the absence of HLA-DM (34, 35). To verify that loss of CLIP from the cell surface was not due to differences in HLA-DM expression, we stained protease inhibitor-treated CD4+ T cell clones for intracellular HLA-DM. HLA-DM expression remained constant, while CLIP expression decreased in these cells (Fig. 5F). Although the possibility remains that changes in HLA-DM localization or kinetic activity could impact peptide editing, there is no evidence to date that protease inhibitors affect such action. We therefore conclude that short-term inhibition of CatS activity in activated CD4+ T cell clones results in down-regulation of cell surface CLIP but not reduction of total class II MHC.

**Cathepsins B, L, and S are differentially expressed in CD4+ T cell clones and BCL**

Cysteine proteases other than CatS have been implicated in both invariant chain proteolysis and peptide epitope generation (18, 36, 37). We wished to identify differences in lysosomal protease expression and activity that could contribute to class II MHC processing in CD4+ T cells, as compared with B cells. We focused our work on cathepsins B, L, and S, as these lysosomal cysteine proteases have been implicated in class II MHC processing and presentation (38) and are also expressed in CD4+ T cells (Fig. 6A and Fig. 7A). We found that resting CD4+ HLA-DR+ T cell clones express less CatS mRNA (Fig. 6A) and contain less CatS activity (Fig. 6B) than donor-matched BCL. We verified these patterns of expression in cells ex vivo and confirmed that peripheral blood HLA-DR+ CD4+ T cells contained fewer CatS transcripts and less active CatS than CD19+ B cells (Fig. 6, C and D).

Conversely, CD4+ T cell clones expressed more CatB and CatL message and activity than BCL, but this significant difference in expression could not be extended to ex vivo cell populations (Fig. 6, C and D; Fig. 7; data not shown). Furthermore, CatL transcripts were only found in a subset of CD4+ T cell clones; lack of CatL mRNA did not correlate with the absence of cell surface HLA-DR on a given clone.
HLAG-DR\(^{+}\)CD4\(^{+}\) T cells ex vivo express less CLIP than CD19\(^{+}\) T cells

We observed that HLAG-DR\(^{+}\)CD4\(^{+}\) T cells express less active CatS than CD19\(^{+}\) B cells (Fig. 4, C and D). To determine the consequence of this reduced CatS expression on CLIP presentation in these cells, we stained for cell surface CLIP in peripheral blood. HLAG-DR\(^{+}\)CD4\(^{+}\) T cells ex vivo express less cell surface CLIP than HLAG-DR\(^{+}\)CD19\(^{+}\) B cells (12.4 ± 0.3 vs 60.4 ± 0.1 CLIP MFI, mean ± SEM, n = 3) (Fig. 8). The low level of CLIP expression on HLAG-DR\(^{+}\)CD4\(^{+}\) T cells was not due to overexpression of HLAG-DM in this subset (Fig. 8A). Indeed, intracellular HLAG-DM expression was lower in CD4\(^{+}\) T cells than in CD19\(^{+}\) B cells. These data suggest that the modest CatS activity in HLAG-DR\(^{+}\)CD4\(^{+}\) T cells is not sufficient to maintain CLIP on the cell surface, while CD19\(^{+}\) B cells, which express higher levels of CatS, constitutively express cell surface CLIP.

**Discussion**

HLAG-DR expression on CD4\(^{+}\) T cells was observed several decades ago, but the mechanisms of class II MHC proteolytic regulation in these cells remain undefined. With the use of protease inhibitors, we examined the requirements for successful Ii processing and class II MHC complex presentation in constitutively HLAG-DR\(^{+}\)CD4\(^{+}\) T cell clones. Our results demonstrate that CatS is crucial for Ii proteolysis in these cells. Specific inhibition of CatS with low concentrations of LHVS resulted in the formation of Ii cleavage intermediates and blocked the successful generation of \(\alpha\beta\)-peptide complexes (Fig. 4).

Furthermore, we find that down-regulation of CatS in early activated HLAG-DR\(^{+}\)CD4\(^{+}\) T cells results in the loss of CLIP from the cell surface but does not significantly reduce total class II MHC presentation (Fig. 5). Therefore the prevailing consequence of variable CatS expression is alteration of the peptide repertoire: HLAG-DR\(^{+}\)CD4\(^{+}\) T cells both in vitro and ex vivo express less CatS and therefore maintain less CLIP on the cell surface than donor-matched B cells (Figs. 6 and 8). A lower level of CatS expression in CD4\(^{+}\) T cells does not necessarily precipitate equivalently low class II MHC expression. It is likely that alternative mechanisms of class II MHC regulation such as complex trafficking and targeted degradation also contribute to expression levels and are differentially active in B cells and T cells. In fact, our data suggest that reduction of class II MHC expression in T cells
postactivation is predominantly controlled by a mechanism other than CatS down-regulation (Fig. 5).

CatS activity alone does not account for limited expression of class II MHC within the CD4+ T cell population, as the majority of CD4+ T cells ex vivo do not express the CIITA (data not shown). Our data indicates, however, that in CD4+ T cells that do express class II MHC CatS regulates nascent class II MHC complex formation.

HLA-DR+ CD4+ T cells in peripheral blood, while rare, do include a functionally distinct subset of CD25high FoxP3+ natural regulatory T cells (10) and are up-regulated in patients with autoimmune disease (6) and HTLV-I (39). HLA-DR is also expressed on activated T cells, although activation alone is not sufficient to induce HLA-DR expression (10). Although the function of class II MHC on these cells remains uncertain, presentation of class II-restricted Ag by T cells has been implicated in anergy induction (40). Additionally, conserved regions of HLA-DR have been reported to bind the immunoregulatory receptors LAG-3 (CD223) (41) and Tirc7 (42).

Whatever functional role HLA-DR ultimately plays in immune modulation, the ability of this ligand to bind the TCR of CD4+ T cells is axiomatic. Identification of the peptides presented by these cells may lend some insight into the target and functional outcome of T-T presentation. Because HLA-DR+ CD4+ T cells lack any known mechanism for professional Ag acquisition, these cells are believed to present self-peptide or T cell tropic viruses (24, 43). An abundance of endogenous peptide in the MHC binding pocket is not unique to the HLA-DR+ CD4+ T cell. In professional APC, endogenous peptide encompasses a significant fraction of the immunosynapse (44). The II fragment CLIP is the most predominant self-peptide presented via class II MHC and in human dendritic cells; CLIP-MHC complexes are up-regulated following inflammatory stimuli (45). We were therefore surprised to observe that HLA-DR+ CD4+ T cells express less cell surface CLIP than B cells and that CLIP expression decreased following activation (Figs. 5 and 7). Our findings demonstrate that class II MHC presentation in CD4+ T cells is not restricted to CLIP, and suggest that CLIP expression is differentially regulated in T cells as compared with professional APC. Thus, the repertoire of endogenous protein bound to T cell MHC products may be more complex than has previously been suggested (3).

We identified differences in lysosomal protease expression between T and B cells that may lead to the generation of different peptide pools available for class II MHC binding. CD4+ T cells do not express AEP (Fig. 3), the only protease to date shown to be requisite for the generation of an antigenic peptide (46), and can express both CatL and CatV (Fig. 7, data not shown). This proteolytic profile, however, is not dissimilar from that of B cells ex vivo (47). Furthermore, the contribution of these proteases to the self-peptide repertoire remains to be seen.

HLA-DR+ CD4+ T cells are nontraditional APC that may play a role in dampening, rather than promoting, immune activation in the human system via class II MHC. Our work demonstrates that, like professional APC, CD4+ T cells possess the processing machinery required for class II MHC:peptide complex formation and that this machinery is regulated postactivation to modulate peptide presentation. Furthermore, our observations establish CatS as the major II processing enzyme in T cells.

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Disclosures
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