

# [Regulation of mhc class ii-peptide complex expression by ubiquitination](https://assignbuster.com/regulation-of-mhc-class-ii-peptide-complex-expression-by-ubiquitination/)

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Major histocompatibility complex class II molecules (MHC-II) function by presenting processed antigens, derived primarily from exogenous sources, to CD4 + T-lymphocytes. MHC-II molecules thereby are critical for the initiation of the antigen-specific immune response. MHC-II is constitutively expressed by immune cells including B cells, monocytes, macrophages, and dendritic cells (DCs) and even non-hematopoietic cells can express MHC-II under inflammatory conditions. While each of these MHC-II-bearing cell types function as “ professional” antigen presenting cells (APCs), DCs have received much attention as APCs since it is these APCs that are able to stimulate naïve antigen-specific CD4 + T cells. Tissue-resident DCs have often been referred to as the “ sentinels of the immune system,” and it is their job to continuously sample their microenvironment by internalizing extracellular fluid and generating peptide-MHC-II complexes (pMHC-II) that can potentially interact with antigen-specific T cells ( [1](#B1) ). While resting (immature) DCs do express considerable amounts of pMHC-II on their surface, stimulation of DCs by a variety of inflammatory stimuli results in increased expression of pMHC-II at the plasma membrane by at least two mechanisms: (1) by increasing antigen proteolysis/peptide binding to MHC-II ( [2](#B2) , [3](#B3) ) and (2) by promoting pMHC-II movement from intracellular antigen processing compartments to the cell surface ( [4](#B4) , [5](#B5) ). Activation of DCs transiently increases MHC-II synthesis and increases macropinocytosis. However, within hours of the activation signal CIITA synthesis (and thus MHC-II synthesis) is severely reduced and macropinocytosis is terminated ( [6](#B6) , [7](#B7) ). Together, these processes poise the recently activated DC to generate large amounts of pMHC-II with antigens derived from pathogens at the site of infection, thereby enhancing their ability to stimulate antigen-specific CD4 + T cells.

At steady-state, the rate of generation of pMHC-II complexes in immature DCs is equal to the rate of pMHC-II degradation. It is regulation of pMHC-II degradation that is the topic of this mini-review. Recently, it has been shown that ubiquitination participates in pMHC-II degradation ( [8](#B8) , [9](#B9) ). MHC-II is ubiquitinated on a single conserved lysine in the cytoplasmic domain of the MHC-II β-chain present in mouse I-A and I-E molecules as well as human HLA-DR molecules, heretofore referred to as K225. The membrane-associated RING-CH-domain containing E3 ubiquitin ligase March-I is the sole E3 ligase responsible for the ubiquitination MHC-II in B cells and is the primary E3 ligase responsible for ubiquitination of MHC-II in DCs ( [10](#B10) ). March-I expression is highly enriched in secondary lymphoid tissues such as spleen and lymph node ( [11](#B11) ) and appears to be especially prominent in APCs such as B cells ( [10](#B10) ), DCs ( [12](#B12) – [14](#B14) ), and monocytes ( [15](#B15) ).

Expression of March-I leads to the down-regulation of several surface molecules including MHC-II, CD86, and transferrin receptor (TfR) ( [11](#B11) , [16](#B16) ). In March-I-deficient B cells, MHC-II expression is much higher than in control B cells, and this effect was mediated by ubiquitination of K225 in the I-A β-chain ( [10](#B10) ). Gain-of-function experiments in which March-I was overexpressed in MHC-II-expressing HeLa-CIITA cells or human monocyte-derived DCs (MoDC) resulted in profound down-regulation of surface HLA-DR level in these cells ( [14](#B14) , [16](#B16) ). Our own loss-of-function experiments revealed that expression of MHC-II was significantly higher on immature DCs isolated from March-I KO mice than on DCs isolated from WT mice. Essentially identical results were obtained using DCs isolated from MHC-II K 255 R ubiquitination-mutant mice, demonstrating that ubiquitination of MHC-II K225 by March-I regulates MHC-II surface expression ( [14](#B14) ).

Whereas March-I is constitutively expressed in resting professional APCs, March-I can be induced or repressed by different stimuli both *in vitro* and *in vivo* . Infection of mouse macrophages with *Francisella tularensis* induces the ubiquitin-dependent degradation of MHC-II by promoting IL-10-dependent March-I expression ( [17](#B17) ). IL-10 up-regulate March-I expression and MHC-II ubiquitination not only in mouse macrophages but also in human monocytes and mouse B cells ( [18](#B18) , [19](#B19) ). Curiously, although most MHC-II-expressing APCs constitutively express March-I, interferon-gamma-treatment of monocytes, which leads to MHC-II expression, does not result in March-I expression unless the cells are also treated with IL-10, highlighting the complexity of March-I expression in APCs. Curiously, the ability of IL-10 to downregulate MHC-II expression in DCs is due to induction of March-I ( [15](#B15) , [20](#B20) ). Perhaps more important than the up-regulation of basal March-I expression, March-I mRNA expression is significantly reduced when resting APCs are stimulated with toll-like receptor (TLR) signals such as LPS, PGN, poly (I: C) ( [16](#B16) , [21](#B21) ). The March-I protein has a half-life of less than 30 min, potentially regulated by auto-ubiquitination ( [12](#B12) ), therefore the termination of March-I mRNA expression leads to a rapid drop in March-I protein levels ( [16](#B16) ). The reduction of March-I protein expression upon DC activation has profound consequences for MHC-II ubiquitination, for upon DC activation MHC-II ubiquitination is dramatically reduced ( [8](#B8) – [11](#B11) , [21](#B21) ). As will be discussed below, it is the activation-induced termination of March-I expression that primarily regulates MHC-II surface expression in DCs.

The available evidence shows that ubiquitination by March-I is an important regulator of MHC-II degradation. Simple overexpression of March-I dramatically reduces the survival of MHC-II molecules in HeLa-CIITA cells and in B cells ( [10](#B10) , [14](#B14) , [16](#B16) ). In addition, studies in mutant mice have shown that surface MHC-II expression is higher and the half-life of MHC-II is significantly prolonged in B cells isolated from March-I KO mice as compared to WT mice ( [10](#B10) ). A similar role for human March-I in regulation of HLA-DR expression MoDCs has also been described ( [16](#B16) ). We have shown that surface pMHC-II complexes on March-I KO DCs or K 255 R ubiquitination-mutant immature DCs are considerably more stable than those in WT DCs and kinetic analyses demonstrated that ubiquitination directly affects the rate of degradation of surface pMHC-II ( [14](#B14) ). Limiting lysosomal proteolysis delays March-I-induced MHC-II degradation in DCs ( [9](#B9) ), suggesting that ubiquitinated MHC-II is degraded in late endosomes/lysosomes in these cell types.

In immature DCs, a relatively large pool of MHC-II is present in intracellular antigen processing compartments. During TLR-mediated DC activation many of these MHC-II molecules traffic to and accumulate on the plasma membrane ( [3](#B3) ). Maturation of DCs not only inhibits fluid-phase macropinocytosis in DCs ( [22](#B22) , [23](#B23) ), but also inhibits the kinetics of MHC-II endocytosis from the cell surface in human MoDCs ( [6](#B6) ). The findings that MHC-II is (1) ubiquitinated in immature DCs, (2) internalizes efficiently in immature DCs, and (3) accumulates intracellularly in immature DCs (but not mature DCs) has led to speculation that ubiquitination regulates MHC-II endocytosis in DCs. It has been shown that anti-MHC-II mAb accumulate intracellularly in WT immature DCs but not in K 255 R ubiquitination-mutant immature DCs ( [8](#B8) , [9](#B9) , [14](#B14) ), a finding that is consistent with the hypothesis that ubiquitination regulates MHC-II endocytosis.

However, the role of ubiquitination in enhancing the kinetics of MHC-II internalization remains controversial. De Gassart et al. have reported that MHC-II internalization was reduced by 50% in MoDCs in which March-I expression was reduced by transfected siRNA ( [16](#B16) ). By contrast, our own studies in both human and mouse DCs have shown that while MHC-II endocytosis is slightly more rapid in immature DCs than in mature DCs, there is no difference in the kinetics of MHC-II endocytosis in DCs from WT, March-I KO, and MHC-II K 255 R ubiquitination-mutant mice ( [14](#B14) ). Furthermore, analysis of March-I-deficient B cells revealed that the internalization rate of MHC-II in March-I KO B cells was similar to that in WT B cells, demonstrating that MHC-II ubiquitination is not required for internalization of MHC-II in B cells ( [10](#B10) ). We have also examined the kinetics of endocytosis of MHC-II in HeLa-CIITA cells expressing (or not) March-I. In agreement with our results in DCs, we found no difference in the rate of MHC-II endocytosis in HeLa-CIIA cells expressing GFP alone or GFP-March-I, demonstrating that ubiquitination of MHC-II does not affect the kinetics of MHC-II endocytosis in DCs ( [14](#B14) ). These data showing that ubiquitination does not affect MHC-II endocytosis rate are also consistent with similar types of experiments showing that ubiquitination profoundly affects the intracellular distribution of fibroblast growth factor receptor 1 and epidermal growth factor receptor but does so without affecting the kinetics of receptor endocytosis ( [24](#B24) , [25](#B25) ).

Despite the significant effects of March-I on pMHC-II ubiquitination and pMHC-II localization, we do not yet have a clear understanding of how ubiquitination actually regulates the stability of pMHC-II complexes. Recently it has been found that the MHC-II polyubiquitin chain length is different in DCs and in B cells and that longer polyubiquitin chains (such as those present in DCs) promote more efficient MHC-II lysosomal targeting ( [26](#B26) ). How polyubiquitin chain length is regulated in APCs (whether by diminished ubiquitination or enhanced activity of deubiquitinating enzymes) remains to be determined. Clearly ubiquitination of MHC-II regulates MHC-II surface expression, and while our own data argues that ubiquitination does not directly affect pMHC-II endocytosis rate, the possibility exists that ubiquitination affects MHC-II surface expression by regulating the ability of pMHC-II to recycle back to the plasma membrane after endocytosis. pMHC-II complexes continuously internalize and recycle from early endosomes to the plasma membrane and back again ( [27](#B27) ). While analysis of internalization rate data has suggested that pMHC-II recycling rates are different in immature DCs and mature DCs ( [6](#B6) ), we have been unable to find direct experimental data to support this theory. We have recently shown that internalized pMHC-II enters into elongated Arf6 + Rab35 + tubular recycling endosomes and efficiently recycles back to the plasma membrane in HeLa-CIITA cells as well as in APCs ( [28](#B28) ). Although a direct link between pMHC-II recycling and ubiquitination has not been established, it is curious to note that overexpression of March-I promotes the re-distribution of MHC-II from early endocytic compartments to terminal lysosomes ( [16](#B16) ) and also that MHC-II co-localizes with recycling TfR + endosomes more in March-I-deficient B cells as compared to WT B cells ( [10](#B10) ). Furthermore, overexpression of the related MARCH family member MARCH-8 alters the itinerary of proteins internalized by clathrin-independent endocytosis from recycling endosomes to terminal lysosomes ( [29](#B29) ), leading to the possibility that ubiquitination of pMHC-II by March-I serves to limit recycling and promote lysosomal degradation of pMHC-II complexes.

## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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