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## TAX1BP1 a novel player in antigen presentation

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CD4<sup>+</sup> T lymphocytes play a major role in establishing and maintaining antiviral immunity. They are activated by antigenic peptides derived from extracellular or newly synthesized (endogenous) proteins presented by the MHC-II molecules. Little is known about the mechanisms leading to endogenous MHC-II-restricted antigen presentation. We recently revealed a novel function of the macroautophagy/autophagy receptor (AR), TAX1BP1, in the presentation of endogenous viral antigens to CD4<sup>+</sup> T cells. In this punctum, we will focus on MHC-II-restricted endogenous antigen presentation and the involvement of TAX1BP1 in the biology of MHC-II molecules.

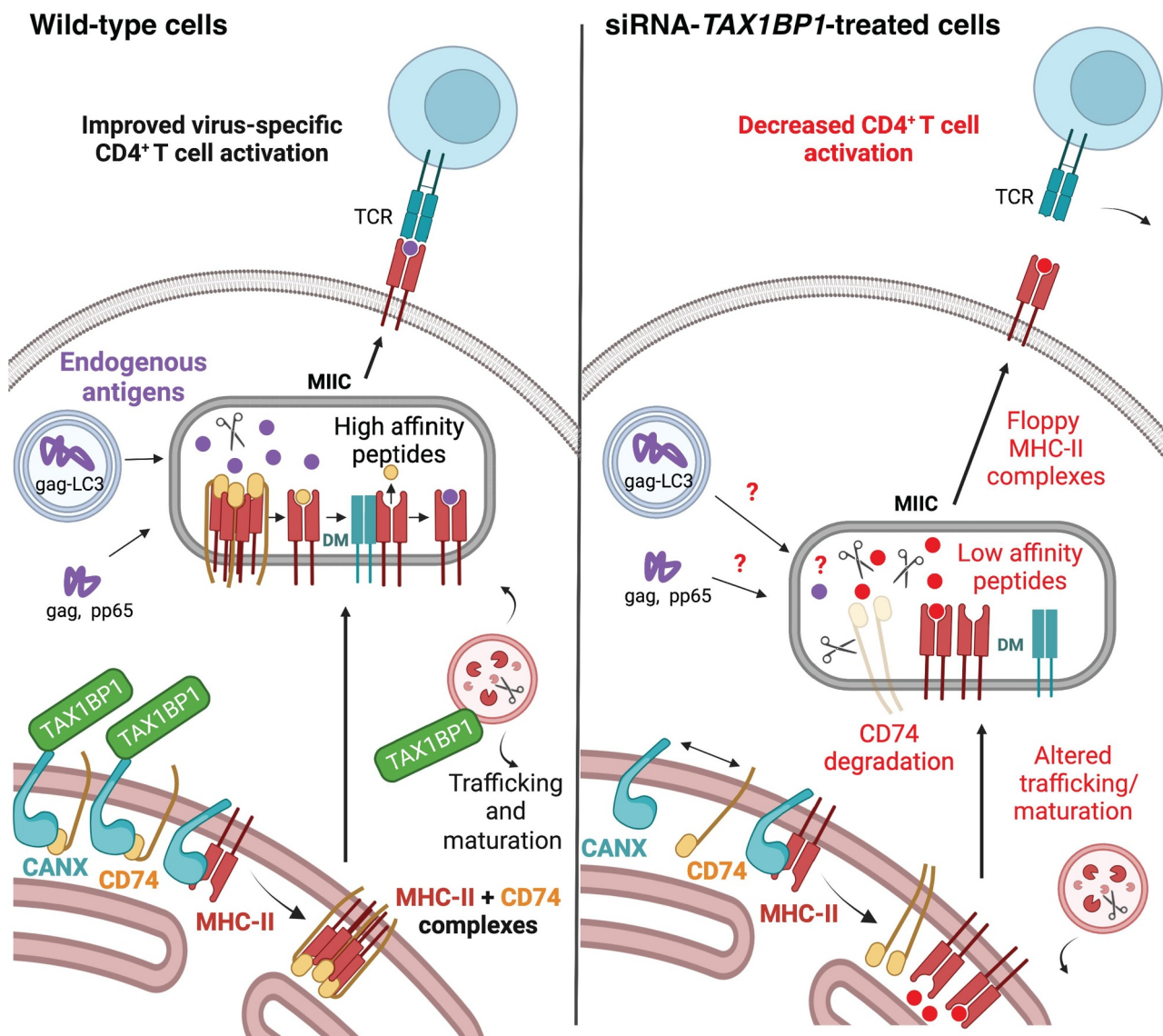
CD4<sup>+</sup> T cells govern the quality of antibody responses and provide help to mount long-lasting cytotoxic CD8<sup>+</sup> T cell responses. However, it is also clear that CD4<sup>+</sup> T cells can exert a direct cytotoxic effect on virus-infected cells and can also infiltrate tumors. It is generally assumed that peptide presented by MHC-II molecules are solely derived from extracellular viral proteins that are captured by phagocytosis or receptor-mediated endocytosis. However, since the eighties, we know that MHC-II molecules can present newly synthesized self- and virus-derived peptides after lysosomal proteolysis. More recently, it was shown that CD4<sup>+</sup> T cell responses to influenza virus are mainly driven by peptides derived from intracellular antigens within antigen presenting cells (APCs). The pathways leading to the loading of MHC-II molecules with endogenous antigens remain poorly characterized. One unresolved issue is how cytosolic antigens are transported into MHC-II-loading compartments (MIIC) that are ill-defined late endo-lysosomal intracellular vesicles.

The pathways of autophagy are obvious candidates that can potentially feed the MIIC with endogenous peptides. The characterization of the MHC-II immunopeptidome, meaning the repertoire of peptides presented by MHC-II molecules, revealed that macroautophagy (herein referred to as autophagy) contributes to the processing of cytoplasmic and nuclear antigens. Using *in vivo* models, several labs established that autophagy participates in the generation of endogenous MHC-II-restricted antigenic peptides and strongly influences thymic selection of auto-reactive CD4<sup>+</sup> T cells. Further evidence that autophagy plays a role in endogenous antigen

presentation comes from *in vitro* studies using APCs transfected with mRNAs or cDNAs encoding tumor or viral antigens targeted to phagophores. However, overall, there are few examples showing endogenous degradation of native tumor or viral antigens to be dependent on autophagy. In fact, autophagy effectors may directly or indirectly affect MHC-II-restricted antigen presentation by regulating, for instance, the delivery of proteases into the MIIC. The molecular links between autophagy and MHC-II-restricted antigen presentation, in particular the mechanisms allowing the delivery of autophagy-degraded antigens to the MIIC, remain poorly defined.

In our recent work [1], we hypothesized that the ARs may contribute at various, so far unknown, levels to MHC II-restricted viral antigen presentation. ARs, in particular CALCOCO2/NDP52, OPTN, SQSTM1/p62, NBR1 and TAX1BP1, target intracellular compounds (e.g., mitochondria, bacteria) or protein aggregates into phagophores, the precursors to autophagosomes, in a process called selective autophagy. In addition, some ARs also regulate signaling pathways and the maturation/trafficking of intracellular vesicles. TAX1BP1, CALCOCO2 and OPTN, for instance, are required for the maturation of autophagosomes whereas TAX1BP1, CALCOCO2, and SQSTM1/p62 orchestrate the maturation of early endosomes into late endosomes.

To study the role of ARs in endogenous presentation, we used siRNA targeting CALCOCO2, OPTN, SQSTM1/p62 and TAX1BP1. Solely silencing TAX1BP1 leads to dramatic reduction of antigen-specific CD4<sup>+</sup> T cell activation. Further highlighting that ARs exert multiple redundant but also exclusive roles. We used a variety of native viral (e.g., HIV-Gag and pp65 proteins from HIV-1 and HCMV, respectively) and model antigens targeted or not to phagophores (HIV-Gag fused to LC3 or LC3<sup>G120A</sup>, respectively) and highlighted that TAX1BP1 affects antigens whose processing is dependent on or independent of autophagy degradation (Figure 1). To get a broader view on the influence of TAX1BP1 on the peptide repertoire bound to MHC-II molecules, we used an MS-based immunopeptidomic approach and showed that TAX1BP1 expression has a major influence on the diversity but also on the affinity of MHC-II ligands. Interestingly, a functional



**Figure 1.** The autophagy receptor TAX1BP1 stabilizes the invariant chain (CD74) and regulates MHC-II trafficking, thereby favoring the presentation of high-affinity peptides to virus-specific CD4<sup>+</sup> T cells: 1) TAX1BP1 loss prevents the activation of HIV- and HCMV-specific CD4<sup>+</sup> T cell clones; 2) TAX1BP1 expression affects the quality and the diversity of peptides presented by MHC-II molecules; 3) TAX1BP1 interacts with the cytoplasmic tail of CANX to favor MHC-II molecule chaperoning by the invariant chain (CD74); 4) in the absence of TAX1BP1, CD74 is degraded; 5) CANX silencing replicates TAX1BP1 deficiency by decreasing CD4<sup>+</sup> T cell activation and exacerbating CD74 degradation.

enrichment analysis of the identified peptides did not reveal a major influence of TAX1BP1 silencing on the cellular distribution of the source protein of MHC-II ligands. Overall, these results suggested that the selective targeting of antigens to phagophores by TAX1BP1 is probably not at play.

To decipher the underlying molecular mechanisms, in TAX1BP1-silenced cells, we then analyzed various steps of MHC-II molecule trafficking, loading and functions. We revealed that TAX1BP1-silencing induces an exacerbated degradation of the invariant chain (CD74/Ii), which might at least partially explain the perturbation of the immunopeptidome. CD74 is indeed a major actor in the biology of MHC-II molecules dictating the folding of the  $\alpha\beta$ MHC-heterodimer, their trafficking to late endosomes and the affinity of peptides loaded onto MHC-II molecules (Figure 1). Importantly, the stability of CD74 is itself

regulated by the ER chaperone CANX (calnexin). Consequently, we performed imaging of intracellular vesicles (in particular MHC-II<sup>+</sup> compartments) and we studied the fate of molecules (HLA-DM, CD74/Ii) involved in MHC-II molecule loading and trafficking. We observed that TAX1BP1 silencing influences  $\alpha\beta$ MHC heterodimer stability, the positioning of late endosomes (including MHC<sup>+</sup> HLA-DM<sup>+</sup> vesicles), lysosomes and autophagosomes (Figure 1). Importantly, in an MS-based interactome, we identified CANX as a binding-partner of TAX1BP1. Thereafter, because CANX is also known to bind CD74, we decided to focus on the role of CANX, to provide insights on one of the mechanisms of action of TAX1BP1. We readily demonstrate, that TAX1BP1 interacts with CANX in various APCs and binds its cytosolic tail (Figure 1). Finally, we provide the first direct

demonstration that in human cells CANX-silencing induces CD74 degradation and inhibits MHC-II-restricted antigen presentation, thus replicating the functional consequences of TAX1BP1 silencing.

In summary, we identified TAX1BP1 as a key player in MHC-II-restricted antigen presentation and CD4<sup>+</sup> T cell immunity. Our study opens new avenues for research, both in the functions of ARs in MHC-II biology and in the study of viruses that might target ARs to escape immune recognition by CD4<sup>+</sup> T cells.

### Disclosure statement

No potential conflict of interest was reported by the author(s).

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