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Spotlight on TAP and its vital role in antigen presentation and cross-presentation

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Abstract

In the late 1980s and early 1990s, the hunt for a transporter molecule ostensibly responsible for the translocation of peptides across the endoplasmic reticulum (ER) membrane yielded the successful discovery of transporter associated with antigen processing (TAP) protein. TAP is a heterodimer complex comprised of TAP1 and TAP2, which utilizes ATP to transport cytosolic peptides into the ER across its membrane. In the ER, together with other components it forms the peptide loading complex (PLC), which directs loading of high affinity peptides onto nascent major histocompatibility complex class I (MHC-I) molecules that are then transported to the cell surface for presentation to $CD8^+$ T cells. TAP also plays a crucial role in transporting peptides into phagosomes and endosomes during cross-presentation in dendritic cells (DCs). Because of the critical role that TAP plays in both classical MHC-I presentation and cross-presentation, its expression and function are often compromised by numerous types of cancers and viruses to evade recognition by cytotoxic CD8 T cells. Here we review the discovery and function of TAP with a major focus on its role in cross-presentation in DCs. We discuss a recently described emergency route of noncanonical cross-presentation that is mobilized in DCs upon TAP blockade to restore CD8 T cell cross-priming. We also discuss the various strategies employed by cancer cells and viruses to target TAP expression or function to evade immunosurveillance - along with some strategies by which the repertoire of peptides presented by cells which downregulate TAP can be

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targeted as a therapeutic strategy to mobilize a TAP-independent CD8 T cell response. Lastly, we discuss TAP polymorphisms and the role of TAP in inherited disorders.

Keywords

Transporter Associated with Antigen Processing (TAP); Antigen-presentation; Cross-presentation; Cytotoxic T Lymphocytes (CTL); Antigen presenting cell (APC); Immune evasion

Introduction

The presentation of peptides on the surface of cells in the context of major histocompatibility complex class I (MHC-I) molecules allows $CD8^+$ T cells to monitor the body for intracellular infection and mutations. In the classical pathway of MHC-I presentation, occurring in every nucleated cell (Richard and Gilkeson, 2018), peptides are generated from endogenous proteins through the actions of proteasomes in the cytoplasm. These peptides are then transported into the lumen of the endoplasmic reticulum (ER) and loaded onto nascent MHC-I molecules for subsequent presentation on the cell surface (Figure 1). For a $CD8^+$ T cell to respond to a peptide derived from an intracellular pathogen or mutated protein, it must first become activated by a professional antigen presenting cell (APC), usually a dendritic cell (DC) (Huang et al., 1994). During cross-presentation, an exogenous antigen is first internalized by a professional APC from the extracellular space through either endocytosis or phagocytosis – depending on the size of the particulate. Such antigens can be derived from a pathogen, a pathogen-derived protein, or a dead cell that is infected or malignant, and can also be derived from soluble proteins or cell-associated proteins from cells undergoing apoptosis. The cross-presentation of self-derived antigens at steady state contributes to the establishment of peripheral $CD8^+$ T cell tolerance (J Magarian Blander, 2018; Embgenbroich and Burgdorf, 2018). The internalized antigen is then processed and loaded onto MHC-I molecules by one of two pathways, the vacuolar pathway or the cytosolic pathway (J Magarian Blander, 2018; Embgenbroich and Burgdorf, 2018; Shen and Rock, 2006) (Figure 1). In the vacuolar pathway, antigens are degraded into peptides in the endosomal/phagosomal compartment by lysosomal proteases such as cathepsin S before being loaded directly onto MHC-I molecules for cross-presentation on the cell surface (Shen and Rock, 2006). In the cytosolic pathway, internalized antigens must be transported from the endosomal/phagosomal compartments into the cytoplasm for proteasomal degradation, followed by TAP-mediated entry back into the nascent endosome/phagosome for loading onto MHC-I molecules. TAP is a 150 kDa heterodimeric protein complex and member of the ATP-binding cassette (ABC) family of transporters (Abele and Tampé, 2004; Lehnert et al., 2016), and is a heterodimer of two proteins, TAP1 and TAP2, both of which are encoded in the MHC class II gene cluster. TAP associates with several other proteins to form the peptide loading complex (PLC), which facilitates the loading of peptides onto MHC-I molecules during both classical MHC-I presentation and cross-presentation of antigens (Cresswell et al., 2005).

In this review, we will focus on the central role of TAP in both the classical pathway of MHC-I antigen presentation and the cross-presentation pathway. We will outline the

history and discovery of TAP and describe how transcriptional initiation from the *Tap1* and *Tap2* genes is controlled by NLRC5, the class I transactivator (CITA). We will describe in detail the MHC-I antigen-presentation pathway, from proteasomal antigen degradation to the TAP-dependent translocation of generated peptides into the ER and loading onto MHC-I molecules, to the final destination at the cell surface for presentation by MHC-I molecules. Differential regulation of the trafficking of MHC-I molecules and the PLC, including TAP will be explained, and we will also address findings that reveal a non-canonical pathway of cross-presentation in the absence of TAP function. Finally, we will describe how both viruses and cancer cells have co-opted the inactivation and/or degradation of TAP as an immune evasion strategy, and will discuss how TAP mutations and polymorphisms are known to impact human health, or have been demonstrated to impact the probability of the development of certain immune-related diseases.

The Discovery of TAP

In the late 1980s, it was already understood that peptides derived in the cytosol were loaded onto MHC-I molecules. However, it was unclear how these peptides were transported into a secretory compartment, then believed to be the ER, in the absence of an ER localization signal peptide (Van Kaer, 2008). In 1989, Alain Townsend proposed the existence of a transmembrane peptide pump that could bring peptides from the cytosol into a secretory compartment in order to be loaded onto MHC-I molecules. This theory was based on experiments that demonstrated that infection with a vaccinia virus that recombinantly expressed a 15 amino acid long influenza nucleoprotein (NP)- derived peptide was sufficient to stimulate NP-specific cytotoxic T lymphocytes (CTL), as well as the existence of ATP-dependent transmembrane peptide transporters (Townsend and Bodmer, 1989). Several studies making use of cell lines, which today are known to be TAP-deficient, demonstrated that exogenous provision of virus-derived peptides in these cells enabled MHC-I molecules to associate with beta-2 microglobulin (β_2M) and reach the cell surface (Cerundolo et al., 1990; Hosken & Bevan, 1990; Townsend et al., 1989). In December of 1990, four papers were published describing genes that could be responsible for the transport of peptides intracellularly across the ER membrane, as originally proposed by Townsend (E. V Deverson et al., 1990; Monaco et al., 1990; Spies et al., 1990; Trowsdale et al., 1990). Two such papers made use of cosmid clones to screen the MHC class-II region of either mice or rats, leading to the discovery of two homologous genes which themselves had a high degree of homology to the ABC transporter family (E. V. Deverson et al., 1990; Monaco et al., 1990). Another group discovered what would eventually be called *Tap1* was upregulated when a cell line was treated with interferon-γ (IFN-γ) and had homology to ABC transporters (Trowsdale et al., 1990). Lastly, one of these papers relied on a same mutant cell line that had previously been shown to require exogenous peptide for the surface expression of MHC-I, and mapped the mutation to a gene homologous to ABC transporters (Hosken and Bevan, 1990; Spies et al., 1990). In 1991, the World Health Organization (WHO) Nomenclature Committee for factors of the human leukocyte antigen (HLA) system convened and decided to name the two genes *Tap1* and *Tap2*, based on their likely function and homology to other ABC transporters (Allen et al., 1991). Following the identification and naming of these two genes, it was demonstrated that the proteins are expressed as a

heterodimer (Kelly et al., 1992; Spies et al., 1992), can be localized to the ER and cis-Golgi (Kleijmeer et al., 1992), and together, are sufficient and necessary to rescue the MHC-I antigen presentation defect observed in the TAP-deficient cell line called T2 (Kaer et al., 1992; Momburg et al., 1992). In 1993, three separate studies demonstrated the mechanism by which TAP1 and TAP2 work together to transport peptides from the cytoplasm to the ER in an ATP-dependent manner (Androlewicz et al., 1993; Neefjes et al., 1993; Shepherd et al., 1993).

The ability to coimmunoprecipitate proteins bound to TAP1 and TAP2 led to further studies that shed light on the mechanism by which TAP delivers peptides from the cytosol to the ER. Immunoprecipitation of MHC-I heavy chain (HC) and β_2M heterodimers led to the discovery that calreticulin is bound to empty MHC-I molecules before they bind to the TAP-associated glycoprotein, now referred to as tapasin and a major component of the PLC, which is required for proper peptide loading to occur (Sadasivan et al., 1996). Further studies of TAP also showed that TAP1 and TAP2 heterodimers preferentially translocated 8-16 amino acid long peptides (Howard, 1995; Momburg et al., 1994). Longer peptides translocated into the ER are further trimmed by ER-associated amino-peptidase associated with antigen processing (ERAAP in mice, ERAP1/2 in humans) for optimal fitting into the peptide binding groove of MHC-I molecules (Hammer et al., 2007; Saric et al., 2002; Serwold et al., 2002). TAP, ERAAP, ERp57, tapasin, calreticulin, as well as the other proteins associated with TAP that facilitate the loading of peptides onto MHC-I molecules, are collectively referred to as the PLC. The PLC, along with other proteins such as chaperone protein and a tapasin homologue, TAP-binding protein-related (TAPBPR) ensure the correct folding and correct peptide loading of MHC-I heterodimers for cell surface expression. While much of the mechanisms underlying peptide loading are now well understood, the consequences of dysfunctional peptide loading caused by mutation, infection, or cancer remain an area of ongoing investigation.

Defining a role for TAP in cross-presentation

Very shortly after its discovery, functional TAP was shown to be necessary for the presentation of exogenously acquired antigen in the form of bead-associated ovalbumin (OVA) protein (Kovacsovics-Bankowski and Rock, 1995). At the time, cross-presentation was poorly understood, but was thought to occur via more than one pathway. There was evidence that antigens could be degraded directly in endosomes/phagosomes, then loaded onto MHC-I molecules in a post-Golgi intracellular compartment for presentation on the cell surface in a TAP-independent manner. It was also believed that internalized antigens could gain access to the cytosol, where they would then be degraded into peptides in the cytosol before transport into the ER for loading onto MHC-I molecules, just as in the classical antigen presentation pathway (Guermonprez et al., 2002). Today, it is understood that in both the cytosolic and vacuolar pathways of cross-presentation, internalized antigens are loaded onto MHC-I molecules in the endosome/phagosome, separately from the ER, although admittedly, direct biochemical evidence for this is still sparse. This requires ER-derived components to be delivered to the endosome/phagosome. In 2002, using microscopy and biochemical approaches, Gagnon *et al.* found that in the J774 macrophage cell line, during phagocytosis, the ER fused with the plasmalemma, in a phosphatidylinositol 3-kinase

(PI3K) dependent process (Gagnon et al., 2002). This discovery was then extended to cross-presenting DCs, in which it was found that soon after phagocytosis, TAP1 and all other components of the PLC could be recovered from phagosomes, along with MHC-I molecules. For cross-presentation of bead-associated protein cargo to occur, TAP was required (Ackerman et al., 2003; Guermonprez et al., 2003). It was also shown that after internalization, soluble antigen that had been endocytosed colocalized with components of the PLC in an ER-like compartment, suggesting that ER-fusion played a role in other forms of endocytosis, namely macropinocytosis (Ackerman et al., 2003). These studies demonstrated that the loading of exogenous antigen onto MHC-I took place separately from the ER. Soon after the publication of these studies, work by Touret *et al.* disputed the idea that fusion of large portions of the ER with phagosomes provides them with ER-derived proteins, including MHC-I and the PLC, that could be involved in cross-presentation (Touret et al., 2005). The authors could find no evidence of continuity between the ER and the phagosome, even transiently, and did not find that the ER contributed significantly to the formation of the nascent phagosome. Instead, the authors found evidence for the contribution of the plasmalemma to the membrane of early phagosomes, and this contribution decreased over time as phagosome matured into phagolysosomes. Notably, the authors did not completely rule out the possibility of alternative vesicular traffic from the ER to phagosomes, which could provide phagosomes with the machinery necessary to facilitate cross-presentation.

Today, it is understood that the ER-Golgi intermediate compartment (ERGIC) is the source of TAP and the PLC during cross-presentation, and that vesicular traffic from the ERGIC to antigen-carrying phagosomes relies on Sec22b, a SNARE that interacts with syntaxin-4, a plasma membrane SNARE also present on phagosomes, to facilitate delivery of the PLC and mediate cross-presentation (Figure 2) (Cebrian et al., 2011). Sec22b had previously been proposed to play a role in phagocytosis by macrophages (Becker et al., 2005; Hatsuzawa et al., 2009). Knockdown of Sec22b using shRNA was shown to abrogate recruitment of PLC proteins, including TAP, to the phagosome (Cebrian et al., 2011), and inhibited cross-presentation in DCs without affecting antigen internalization (Cebrian et al., 2011; Nair-Gupta et al., 2014). Knockout of Sec22b in mice, however, showed conflicting data. Some investigators noted results consistent with knockdown studies both in vitro and in vivo in a tumor model (Alloatti et al., 2017), while others saw no impairment in the in vitro cross-presentation of either soluble or phagocytic antigen (Wu et al., 2017). This was likely due to the different experimental strategies used by the two groups (Montealegre and van Endert, 2017), though Wu *et al.* demonstrated that Sec22b shRNA could potentially affect the expression of 23 other genes, some of which may play a role in cross-presentation (Wu et al., 2017).

Regulation of *Tap1* and *Tap2* by NLRC5 and other transcription factors

Even before *Tap1* had been assigned its name, it was known that the expression of the gene was upregulated in cells exposed to IFN-γ (Trowsdale et al., 1990). However, it is now widely believed that the expression of *Tap1* is under the control of NLRC5 (NLR family, CARD domain containing 5/NOD27/CLR16.1), sometimes referred to as the MHC class I transactivator (CITA), and often described as a “master regulator” of the transcription of

MHC-I genes (Sznarkowska et al., 2020). NLRC5 is expressed ubiquitously across various tissues in both mice and humans, though its expression is highest in the hematopoietic compartment (Benko et al., 2010). The expression of NLRC5 is induced when IFN-γ binds to the IFN-γ receptor which activates JAK1/JAK2 signaling. This leads to the activation of a STAT1 homodimer that can bind to the STAT1 binding sites in the NLRC5 promotor (Meissner et al., 2012). It has also been reported that NLRC5 expression can be induced by viral infection, LPS, and poly(I:C) (Benko et al., 2010; Neerincx et al., 2010), as well as by type I IFNs, though less potently than IFN-γ (Tong et al., 2012). Like other genes involved in MHC-I antigen presentation, *Tap1* contains an SXY motif in its promotor region. This genetic element contains binding sites for several transcription factors, including an X-binding regulatory factor X (RFX) complex (Yoshihama et al., 2017), which is bound by the transcription factor RFX5. Binding of RFX5 to this SXY motif is essential for NLRC5 binding to the *Tap1* promotor, and it has been shown that in the absence of *Rfx5* expression, TAP expression is reduced (Ludigs et al., 2015). RFX5 is expressed constitutively, and forms an integral part of the CITA enhanceosome that together with NLRC5 regulates the expression of *Tap1* and other MHC-I related genes (Yoshihama et al., 2017).

Beyond activating the expression of *Tap1* and other genes, NLRC5 has also been shown to contribute to the expression of MHC-I genes by removing histone modifications that decrease the accessibility of the promotor, though this was not shown specifically for the TAP genes (Robbins et al., 2012). In NLRC5-deficient mice, it was observed that mRNA levels of *Tap1* are reduced in the spleen tissue of both healthy mice and mice infected with *Listeria monocytogenes*, and that splenocytes from NLRC5-deficient mice do not upregulate *Tap1* expression to the same degree as those from wild-type mice following LPS stimulation (Yao et al., 2012). While the upregulation of *Tap1* in response to infection or LPS stimulation is reduced in the absence of NLRC5, *Tap1* upregulation is not completely abrogated. This is similar to the expression of MHC-I for which it has been shown that loss of NLRC5 reduces the steady-state levels of the gene, but not its induction by IFN-γ (Robbins et al., 2012).

There are other transcription factor binding sites in the *Tap1* promotor region that could explain the induction of this gene in response to IFN-γ, even in the absence of NLRC5. The promotor contains a gamma interferon activation site (GAS) that can be bound by STAT1, and in the absence of STAT1, *Tap1* gene expression is not induced by IFN-γ in murine bone marrow derived macrophages. The promotor also contains an interferon regulatory factor-1 (IRF-1) binding site, which is important for the induction of *Tap1* in some cell lines (Brucet et al., 2004). Some IRFs are expressed constitutively, so they could also be responsible for the regulation of *Tap1* during homeostasis (Jongsma et al., 2019). The *Tap1* promotor also contains an NF-κB box, which has not been shown to play a role in the regulation of *Tap1* expression in response to IFN-γ (Brucet et al., 2004), though modern tools could soon uncover a role for this binding site (Jongsma et al., 2019).

While NLRC5 is an important inducer of *Tap1* expression, it has not been shown to control the expression of *Tap2*. In the study that first described NLRC5 as a master regulator of the MHC-I antigen-presentation genes, overexpression of NLRC5 in HEK293 cells induced the expression of luciferase when the *Tap1*, but not *Tap2*, promotor was placed upstream of

luciferase (Meissner et al., 2010). This is rather surprising, given the requirement for TAP1 and TAP2 to interact to form a functional TAP heterodimer (Jongsma et al., 2019). While *Tap2* expression is induced by IFN-γ, though to a lesser degree than *Tap1* (Ma et al., 1997), the *Tap2* promotor is unique among genes involved in MHC-I antigen presentation in that it contains only one of the regulatory elements shared among the other genes, an IRF1/IRF2 binding site, which explains how *Tap2* is upregulated in response to IFN-γ (Arons et al., 2001). Taken together, these studies suggest that while NLRC5 is often referred to as the "master regulator" of genes involved in MHC-I antigen presentation, it does not play a singular role in upregulating these genes, particularly *Tap1* and *Tap2* in response to IFN-γ stimulation (Meissner et al., 2010; Robbins et al., 2012; Yao et al., 2012).

From protein, to peptide, to TAP

The function of TAP is to transport peptides derived in the cytosol into the ER or other compartments such as a phagosome to be loaded onto MHC-I molecules. Before a peptide can be translocated by TAP, however, it must be processed in the cytosol, a process which begins with an antigen gaining access to the cytosol. In most cells that facilitate classical MHC-I presentation, those peptides are derived from endogenous proteins that maintain the normal function and structure of a cell, unless a cell is infected by an intracellular pathogen or is expressing a mutated protein. In the case of cross-presentation, peptides presented on MHC-I molecules are derived from exogenous antigens internalized from the extracellular space. This can occur via several different pathways, including endocytosis, micropinocytosis, and phagocytosis. The internalization pathway depends on the size and nature of the antigen being internalized, and on the receptors engaged on the APC's surface during internalization (J Magarian Blander, 2018; Burgdorf and Kurts, 2008). Once an antigen is internalized by the APC, to be cross-presented via the TAP-dependent cytosolic pathway, it must enter the cytosol, a process that is poorly understood, but which may occur though several potential mechanisms. One such mechanism is ubiquitination of the cytosolic domain of the surface receptor engaged by the antigen during endocytosis, such as the mannose receptor, which is thought to recruit p97, a AAA-ATPase, to perhaps support the translocation of endosomal peptides through Sec61, a transmembrane channel (Ackerman et al., 2006; Kaiser and Römisch, 2015; Tretter et al., 2013; Zehner et al., 2011; Zehner and Burgdorf, 2013). Cytosolic entry could also occur by NOX2 proteins inside the endosome producing reactive oxygen species (ROSs) that cause peroxidation and damage to the endosomal lipid membrane, and thus release of endosomal contents into the cytosol (Dingjan et al., 2016). This has recently been shown to occur in the context of dead cells, which engage DNGR-1 (Clec9a) through exposed F-actin myosin complexes, causing activation of the non-receptor tyrosine kinase SYK and subsequently NADPH oxidase activity, which damages the phagosomal membrane causing release of its contents into the cytosol (Canton et al., 2020).

Once in the cytosol, antigens undergo proteasome-mediated degradation into peptide fragments. This process begins when a protein is marked for degradation by the addition of several ubiquitin molecules to its lysine side chains. The protein will then be delivered to the proteasome, a multi-protein, barrel-shaped holoenzyme. The proteasome removes the ubiquitin modules and unravels the 3D structure of the protein before degrading it

into short polypeptide fragments of between 2 and 25 amino acids in length (Goldberg, 2007). Most of these short peptides will be degraded further by cellular peptidases as part of normal cellular housekeeping, but some will be translocated into the ER or other endocytic/phagocytic compartments by TAP. Before discussing the function of TAP, it is important to note that encoded within the MHC class II gene cluster (the same gene cluster that encodes *Tap1* and *Tap2*) are alternative proteasome subunits which, when incorporated in place of the constitutively expressed proteasome subunits, form what is known as the immunoproteasome (Embgenbroich and Burgdorf, 2018; Van Kaer, 2008). When incorporated into the proteasome, these alternative subunits alter the rate of peptide production and cleavage site specificity of the 20S proteasome (Boes et al., 1994; Driscoll et al., 1993; Gaczynska et al., 1993; Groettrup et al., 1995), though recent work has challenged this long held paradigm (Wu et al., 2019). Following proteasomal processing, peptides must be transported from the cytoplasm into a secretory compartment of the cell, be that the ER, an endosome, or a phagosome, in order to be loaded onto MHC-I molecules. Rather than just diffusing through the cytoplasmic space and eventually finding their way to TAP, chaperone proteins such as heat shock protein-90 (hsp90) are thought to shield and shuttle peptides from the proteasome to TAP for transport from the cytosol into a secretory compartment (Callahan et al., 2008).

In the context of cross-presentation, all of the components of antigen processing that have been mentioned thus far have been shown to localize to the phagosome. In experiments using the murine J774 macrophage cell line, ubiquitinated proteins and the proteasome colocalized on the cytoplasmic face of the phagosome, as seen by immunofluorescence microscopy (Houde et al., 2003). These proteins were also detected in immunoblots of phagosomal fractions. This, combined with the observation that phagocytosed fluorescent protein exits the phagosome and enters the cytoplasm, suggests that the phagosome is a completely cross-presentation competent organelle that contains the machinery necessary to mediate the export and processing of proteins into peptides, before they are transported back into the phagosome and loaded onto MHC-I molecules (Houde et al., 2003).

Through TAP to the cell surface

After association with cytoplasmic chaperone proteins, the peptides are eventually brought to TAP, with which they associate in an ATP-independent manner. The exact mechanism of peptide transport through TAP has not yet been fully elucidated, but based on biochemical experiments and structural studies of homologous proteins, a model has been established (Bock et al., 2019; Geng et al., 2015; Lehnert and Tampé, 2017; Procko and Gaudet, 2009). When TAP is not active, the transmembrane domain (TMD) of TAP assumes a closed, inward-facing conformation, with two ATP-Magnesium molecules bound to its cytosolic nucleotide binding domains. When a peptide of sufficient affinity binds to the peptide-binding domain of TAP, a conformational change occurs in the protein. Peptides, which are believed to be in a β-hairpin-like conformation, bind to multiple residues on the cytosolic side of TAP (Geng et al., 2015). Their affinity for TAP is based on multiple factors, including sequence, length, and the specific amino acids located near the N- and C-termini of the peptide (Lehnert et al., 2016). Peptide binding causes the nucleotide binding domains (NBDs) of TAP1 and TAP2 to dimerize and shifts TAP to an outward-facing state, thus

moving the peptide from the cytosolic face of TAP through the membrane. Eventually, the peptide is released into the secretory compartment, which is coupled to ATP-hydrolysis (Abele and Tampé, 2004; Neefjes et al., 1993). Once the peptide enters the lumen and the ATP has been hydrolyzed, exchange of the ADP molecule for an ATP molecule occurs. This resets TAP into a conformation that will allow it to accept and transport another peptide (Lehnert and Tampé, 2017; Procko and Gaudet, 2009).

After a peptide reaches the ER lumen, to be loaded onto an MHC-I molecule, it must be trimmed to an appropriate length. In most cell types, the ER aminopeptidase associated with antigen processing (ERAAP) facilitates this. ERAAP plays an important role in editing the N-terminal end of peptides to generate lengths of 8-10 amino acids that fit into the peptide binding groove of MHC-I molecules (Serwold et al., 2002), though longer peptides can also elicit a $CD8^+$ T cell response (Wu et al., 2019). Like many proteins involved in antigen-presentation, ERAAP expression is IFN-γ inducible (Serwold et al., 2002), and the absence of ERAAP greatly alters the repertoire of peptides presented on the cell surface in the context of MHC-I antigen-presentation. In both mouse and human DCs, a peptide that enters the phagosome/endosome is not trimmed by ERAAP, but by the insulin-regulated endopeptidase (IRAP), a homologous IFN-ɣ inducible endopeptidase, and the only endopeptidase active in these subcellular compartments (Saveanu et al., 2009).

Following trimming by ERAAP or IRAP, a peptide that is of appropriate length and affinity can be loaded onto an MHC-I molecule, which is in complex with the PLC. In cross-presenting cells, the subcellular trafficking of MHC-I molecules and the PLC to a cross-presenting endosome is tightly but differentially regulated, *as discussed in a later section*. Unbound or empty MHC-I molecules are stabilized in a peptide receptive conformation through interaction with the PLC, in particular with the MHC-I molecule chaperone tapasin. Tapasin acts as a vital component of the PLC and mediates the selection of high affinity peptides for binding to MHC-I molecules (Howarth et al., 2004; Wieczorek et al., 2017). Tapasin mediates the interaction between nascent MHC-I molecules and TAP and ensures the formation of robust MHC-I heterodimers through its catalytic activity by exchanging low affinity peptides for high affinity peptides in a process referred to as peptide editing (Praveen et al., 2010; Williams et al., 2002). Tapasin works with calreticulin to prevent improperly loaded MHC-I molecules from leaving the ER (Mak et al., 2014). Mice lacking tapasin on APCs result in a $CD8^+$ T cell response that is more biased toward peptides with lower affinity for MHC-I molecules than in wild-type mice (Boulanger et al., 2010). However, these mice have more than a 100-fold decreased cell surface expression of MHC-I molecules and subsequently severely impaired $CD8^+$ T cell immunity in comparison to wild-type control mice (Garbi et al., 2000; Grandea et al., 2000). The absence of tapasin does not always impact all MHC-I molecule allotypes equally. For instance, HLA-A2 peptides are still be presented on the cell surface in the absence of tapasin, albeit along with many MHC-I molecules in a peptide-receptive or unbound conformation, whilst other HLA haplotypes will be sequestered in the ER (Lewis et al., 1998; Wieczorek et al., 2017). Furthermore, other studies describing the PLC-independent chaperone protein and a tapasin homologue TAPBPR suggest a vital role for this protein in peptide editing and efficient peptide loading onto MHC-I molecules in both classical and cross-presentation of antigens (Boyle et al., 2013; Du Pasquier, 2000). Both tapasin and TAPBPR are IFN-γ inducible

type I transmembrane proteins and may work together, possibly in an antagonistic fashion, to participate in quality control mechanisms ensuring efficient trimming and loading of peptides. Unlike tapasin, TAPBPR does not bind ERp57 or calreticulin and is also found in the *cis*-Golgi network suggesting a role for this protein beyond the ER (Boyle et al., 2013; Hermann et al., 2015). TAPBPR stabilizes unbound MHC-I molecules and prohibits the rebinding of peptides during peptide editing to ensure highly efficient peptide binding to the MHC-I molecule groove (Sagert et al., 2020). Furthermore, TAPBPR associates with UDP-glucose:glycoprotein glucosyltransferase (UGT1/UGGT1) to recycle unbound or sub-optimally bound MHC-I molecules back to the PLC to ensure correct folding, trafficking and cell surface presentation of peptide bound MHC-I molecules (Neerincx et al., 2017). Therefore, TAPBP is a second peptide editor that functions outside of the PLC and represents a vital component of the MHC-I antigen-presentation pathway in cells. Once a high affinity peptide is complexed to the peptide groove of an MHC-I molecule, the transport of the peptide:MHC-I complex to the cell surface can begin (Wearsch and Cresswell, 2008).

While the stability of MHC-I molecules are greatly increased following binding with a high affinity peptide, empty MHC-I molecules do traffic to the cell surface (Springer, 2015). MHC-I molecules accumulate at the ER exit sites prior to loading into COP-II coated ER transport vesicles, which traffic MHC-I molecules to the ERGIC. Once in the ERGIC, peptide:MHC class I molecules undergo further quality control that can scrutinize the stability of the complex, and they are then trafficked further to the *cis*-Golgi. Here, they undergo even more quality control by members of the PLC that can accumulate there, as well as by other proteins like UGGT1 (Springer, 2015). Improperly folded and empty MHC-I heterodimers accumulate in the *cis*-Golgi. This can occur in the absence of functional TAP (Raposo et al., 1995). MHC-I molecules that eventually reach the surface have passed the extensive quality control of the ER-Golgi intermediate compartment (ERGIC) and *cis*-Golgi (Nair-Gupta et al., 2014), as an antibody against properly folded peptide:MHC-I will not show colocalization with the PLC components or ERGIC resident proteins (Kuhns and Pease, 1998).

TAP-independent cross-presentation

While the role of TAP in mediating the transport of peptides from the cytosol to the ER for presentation in the context of MHC-I molecules is well established, the importance of TAP during cross-presentation is still debated. Indeed, there are pathogens, such as *Toxoplasma gondii* (Bertholet et al., 2006) and vaccinia virus (Ramirez and Sigal, 2002) where TAP is thought to be necessary for cross-presentation to occur, while other pathogens, such as *Leishmania major* (Bertholet et al., 2006), can still be cross-presented in the absence of TAP. The discrepancies in the necessity of TAP for cross-presentation are likely based on many factors, one of those being the nature of the antigen, and the pathway by which it is thus internalized. In one study, OVA was conjugated to two types of beads, poly-lactide poly-glycolide (PLGA) beads (OVA-PLGA) or iron oxide beads (OVA beads). While the OVA beads required functional TAP to facilitate cross-presentation, TAP was dispensable for the OVA-PLGA (Shen et al., 2004). Another group found that TAP-knockout DCs infected with OVA-expressing *L. major* could prime OVA-specific OT-I T cells, while when DCs were

administered OVA-coated latex beads, only wild-type DCs could prime OT-I cells, unless the amount of OVA used to coat the beads was increased 15-fold, which suggests that TAP-independent cross-presentation is possible once a certain threshold of antigen concentration is passed (Bertholet et al., 2006). It has also been reported that incubating TAP-deficient DCs at a low temperature can increase the number of MHC-I molecules that reach the surface, and can restore cross-presentation of phagocytosed, particulate antigen, but not of soluble, receptor-targeted endocytosed antigen. This group also found that treatment with protease inhibitors reduced the cross-presentation of phagocytosed antigen, but not the receptor-targeted soluble antigen (Merzougui et al., 2011). The cross-presentation of a long HLA-A1-restricted melanoma antigen MAGE-A3 derived peptide was found to require TAP even though it relied on the vacuolar pathway of cross-presentation (Ma et al., 2019). TAP-dependency was indirect because the cross-presented peptide did not need to be transported by TAP, but rather reflected the importance of TAP in proper folding of nascent MHC-I molecules in the ER such that they may follow a proposed nonclassical secretory route to the vacuole (Ma et al., 2019). On the other hand, the same group found that TAP is not required for the vacuolar cross-presentation of a similarly long melanoma gp100 antigen derived peptide by HLA-A2 (Ma et al., 2016). Based on these observations, the authors cautioned that TAP dependency cannot be equated with cytosolic as opposed to vacuolar cross-presentation. In fact, our group has found that the depletion of MHC-I molecules from the ERC and their mislocalization to the ERGIC in the absence of TAP add a new layer of complexity to the role of TAP in cross-presentation that has to do with the trafficking routes of MHC-I molecules to sites of antigen internalization rather than TAP-mediated transport of cross-presented peptides (Figure 3) (Barbet et al., 2021). Taken together, the studies suggest that the requirement for TAP during cross-presentation may be a reflection of multiple factors including the route of antigen internalization, endocytosis versus phagocytosis, but also the subcellular locations of MHC-I molecules in the presence or absence of TAP function.

Often, when considering the cytosolic cross-presentation pathway, the proteasome is thought to be intrinsically a part of this TAP-dependent pathway. There is, however, data that points to the existence of a proteasome dependent, but TAP-independent pathway. In the study mentioned earlier using a decrease in temperature to increase the number of MHC-I molecules on the surface of TAP-deficient DCs that have been administered phagocytic antigen, that increase in MHC-I expression was found to be proteasome dependent. The authors suggested the existence of a TAP-independent mechanism, such as an alternative peptide transporter, that could import these peptides back into the phagosome following their generation by the proteasome in the cytosol (Merzougui et al., 2011). Later, it was demonstrated that a melanoma peptide known as $PMEL_{209\text{-}217}$ requires proteasomal processing to facilitate its generation and cross-presentation, but does not require TAP (Vigneron et al., 2018). Since then, the same group has demonstrated that proteasomes are actually present in the phagosomes themselves, which would explain one possible mechanism by which cross-presentation can occur in the absence of TAP (Sengupta et al., 2019). This was based on observations that proteasomal components colocalized with $LAMP1^+$ (lysosomes) as observed via confocal immunofluorescence and electron microscopy experiments. They also reported that exogenous expression of β_2M could rescue

the reduction in cross-presentation associated with TAP-deficient APCs, by increasing the available pool of properly folded MHC-I molecules (Sengupta et al., 2019). These observations are in line with earlier studies, described above, that found the proteasome colocalized to the phagosome (Houde et al., 2003). While the localization of the proteasome to the phagosome does not negate the possibility of a peptide transporter other than TAP for use in cross-presentation, these studies demonstrate the confusion surrounding the role of TAP in cross-presentation, and whether it is essential at all for cross-presentation (Sengupta et al., 2019). When interpreting results of studies of TAP-deficiency in cross-presentation, it is also important to consider that TAP assists in the proper folding of MHC-I molecules, which can also impact cross-presentation (Song and Harding, 1996).

Subcellular trafficking of MHC-I molecules for cross-presentation

Prior to its association with β_2M, as it emerges from the Sec61 translocon through which it is co-translationally translocated, the MHC-I HC associates with the chaperones calreticulin and immunoglobulin binding protein (BiP). These chaperones help properly fold and stabilize the nascent polypeptide before it interacts with β_2M, forming a heterodimer that is further stabilized upon interaction with the PLC (Figure 1) (J Magarian Blander, 2018; Blees et al., 2017). Structural studies using Burkitt's lymphoma cells, have revealed the position of TAP in the native structure of the PLC and situates it at the centre of the complex (Blees et al., 2017).

In the context of cross-presentation, in order to facilitate peptide loading, MHC-I molecules and the PLC must intersect with the endolysosomal pathway through which exogenous traffic are routed into the APC. Encoded in the cytoplasmic domain of MHC-I molecules is a highly conserved tyrosine residue that is necessary for the targeting of MHC-I molecules to LAMP-I$^+$ endolysosomal compartments in order to facilitate peptide loading (Lizée et al., 2003). If this tyrosine residue is mutated, DCs become deficient in cross-presentation of the immunodominant OVA epitope and are also unable to prime a robust CTL response against vesicular stomatitis virus (VSV) or Sendai virus (Lizée et al., 2005).

Another important distinction between classical antigen-presentation and phagocytic antigen cross-presentation is that the source of MHC-I molecules in the context of the latter is not the ER, but rather, an endosomal recycling compartment (ERC)-like compartment marked by Rab11a (Nair-Gupta et al., 2014). Despite its name, the source of MHC-I molecules that stocks this Rab11a$^+$ compartment is still unclear, as a recent publication demonstrated that these ERC MHC-I molecules do not recycle from the plasma membrane as has long been suspected (Montealegre and Van Endert, 2019). Knockdown of Arf6, a small GTPase that mediates MHC-I molecule recycling, had no impact on either cross-presentation nor on these intracellular stores of MHC-I molecules in the Rab11a$^+$ compartments (Montealegre and Van Endert, 2019). Regardless of how this compartment acquires MHC-I molecules, our group found that the trafficking of ERC-resident MHC-I molecules to phagosomes carrying antigen is conditional on TLR engagement in the cross-presenting DCs by TLR ligands associated with the phagocytic antigen. Upon TLR-MyD88 signaling, IKK2 is activated and phosphorylates the synaptosomal-associated protein 23 (SNAP23) on phagosomes, thus stabilizing ERC SNARE VAMP3/cellubrevin and VAMP-8/endobrevin interactions

with phagosonal SNAREs and allowing vesicular ERC-to-phagosome trafficking to deliver MHC-I molecules to the cross-presenting phagosome (Figure 2). By contrast, phagosomal trafficking of PLC components from the ERGIC is not controlled by TLR signaling and occurs constitutively through an ER-to-phagosome vesicular pathway dependent on the ER SNARE Sec22b (Alloatti et al., 2017; Nair-Gupta et al., 2014).

Our group has recently demonstrated a second, emergency route of cross-presentation, active when TAP is unable to function (Barbet et al., 2021) (Figure 3). Without functional TAP, the subcellular location of MHC-I molecules changes such that the ERC becomes depleted of MHC-I molecules. Instead, newly generated MHC-I molecules remain in the ERGIC, but can still be recruited to phagosomes. TAP-deficient DCs continue to cross-present coopting instead ER-SNARE Sec22b-mediated traffic from the ERGIC to deliver MHC-I molecules to phagosomes for cross-presentation. This pathway normally delivers the MHC-I PLC to phagosomes to enable cross-presentation (Cebrian et al., 2011; Nair-Gupta et al., 2014). Because vesicular traffic from the ERGIC is not controlled by TLRs (Nair-Gupta et al., 2014), Sec22b-dependent phagosomal MHC-I molecule recruitment and cross-presentation does not follow TLR regulation. As such, in an effort to counter TAP blockade, DCs switch from TLR-regulated cross-presentation to noncanonical cross-presentation that bypasses TLR regulation (Figure 3) (Barbet et al., 2021). As such, although the presentation of peptides by MHC-I molecules is preserved during TAP blockade, this back-up strategy comes at the cost of indiscriminate presentation of peptides from either self or non-self in a T-cell costimulatory context during infection (Barbet et al., 2021).

Besides MHC-I molecules, TAP itself has been shown to undergo subcellular relocalization from endosomes, the sites of internalized antigen, to the ER and lysosomes upon the differentiation of monocytes into immature and mature DCs (Döring et al., 2019). This was associated with increased levels of TAP1, albeit reduced TAP-dependent peptide transport and an increased half-life of cell surface peptide:MHC-I complexes, leading to a model whereby antigen uptake and processing could be spatiotemporally separated to partially explain the greater $CD8^+$ T cell stimulatory capabilities of monocyte derived DCs (Döring et al., 2019).

Targeting TAP by cancer cells to avoid immunosurveillance

Throughout the course of cancer development, cells can gain mutations that aid in cancer survival, propagation, and metastasis. An important step in the development of these mutations is to first evade and suppress the immune system, which can be accomplished by targeting the MHC-I antigen presentation pathway (Margalit, 2007). Because of TAP's central role in translocating peptides, including tumor associated antigens (TAAs) into the ER lumen, tumor stem cells and malignant cells associated with many types of cancer often target TAP as an immune evasion strategy (Abele and Tampé, 2006; Bandoh et al., 2010; Einstein et al., 2009; Fowler and Frazer, 2004; Henle et al., 2017; Johnsen et al., 1999; Kasajima et al., 2010; Leibowitz et al., 2011; Ling et al., 2017, 2017; Marincola et al., 2000; Mehta et al., 2008; Romero et al., 2005; Yang et al., 2020; Ylitalo et al., 2017), thereby reducing peptide loading onto MHC-I molecules and peptide surface presentation to evade recognition by cytotoxic CD8 T cells (Abele and Tampé, 2004). TAP deficiency has been

reported to be more frequent in later stages of cancer, correlating with reduced numbers of tumor infiltrating lymphocytes as well as macrophages, which may explain immune evasion (Ling et al., 2017). Thus, decreased expression levels of TAP can be utilised as an indicator of poor prognosis in patients with cancer (Bandoh et al., 2010; Henle et al., 2017; Ling et al., 2017).

Restoration of CTL-induced eradication of cancer cells that have downmodulated TAP1 and/or TAP2 can be achieved by exogenous expression of the TAP subunits or through treatment with IFN-γ (Agrawal et al., 2004; Raffaghello et al., 2005; Seliger et al., 1998, 1997). This suggests that cancer cells target the transcription of TAP, which, as mentioned earlier, is controlled by IFN-γ signaling (Bach et al., 1997; Meissner et al., 2012; Sznarkowska et al., 2020; Trowsdale et al., 1990). Additionally, the genes that encode the MHC-I antigen presentation machinery are commonly the target of epigenetic modifications such as phosphorylation, acetylation and methylation, which leads to their downregulation and the evasion of immunosurveillance (Baylin and Ohm, 2006; Burr et al., 2019; Cheng et al., 1996; Luo et al., 2018, 2006; Magner et al., 2000; Serrano et al., 2001; Tomasi et al., 2006). Hypermethylation of the CpG sites in the closest promoter region of *TAP1* has been observed in colorectal cancer (Ling et al., 2017) and in head and neck squamous cell carcinoma (Poage et al., 2012), while inhibiting histone deacetylases in melanoma cells has been shown to enhance transcription of TAP1 and TAP2 and elicit an antigen specific T cell response and IFN-γ expression (Khan et al., 2008). Additionally, a recent study reported a link between activation of the Wnt/β-catenin signaling pathway and downregulation of expression of the MHC-I peptide presentation pathway machinery, including TAP1, in glioma stem cells of glioblastoma in both mice and humans (Yang et al., 2020). This resulted in reduced peptide presentation and thus immune evasion as a result of the binding of c-Myc, a transcription factor that lies downstream of β-catenin, to the *TAP1* promotor region and suppression of *TAP1* transcription. This could be reversed by inhibiting histone deacetylase to target c-Myc, which resulted in restoration of a CTL response (Yang et al., 2020). Therefore, epigenetic modifications are another strategy for malignant cells to downregulate TAP, though downregulation of other components in MHC-I antigen presentation may also be necessary to adequately escape immunosurveillance (Khan et al., 2008).

Mutations resulting in either impaired TAP function or the rapid degradation of TAP protein is yet another strategy that malignant cells use to evade and suppress the immune response without affecting TAP transcription (Yang et al., 2003) as observed in small-cell lung carcinoma cells (Chen et al., 1996) and melanoma cells (Seliger et al., 2001). As expected, IFN-γ treatment did not restore TAP function in these cells (Yang et al., 2003), however, transducing lung carcinoma cells with TAP1 expression vectors did restore TAP expression and function, and thus increased the level of MHC-I peptide presentation on the cell surface. The investigators also reported enhanced tumor infiltration by DCs and T cells, which led to increased cross-presentation by DCs and cross-priming $CD8^+$ T cells that secreted TNF-α. This resulted in impaired tumor growth and increased survival in lung tumor or melanoma bearing mice (Lou et al., 2005; Zhang et al., 2007).

In the absence of functional TAP, the presentation of peptides by cancer cells is reduced, though it does not stop altogether. Rather, an alternative repertoire of peptides, termed T cell epitopes associated with impaired peptide processing (TEIPPs) are presented by these TAP deficient cells, and these peptides are still able to activate a functional $CD8^+$ T cell response that leads to tumor regression (Marijt et al., 2019b; van Hall et al., 2006; Wolpert et al., 1997). By starting with a CTL that was capable of lysing tumor cells, then matching that CTL to its target antigen by generating a cDNA library of potential tumor antigens, one of these TEIPPs, preprocalcitonin (ppCT) was discovered, a protein that is highly overexpressed in several lung carcinomas when compared to healthy tissues. The presentation of this peptide was dependent on reduced expression of TAP (Durgeau et al., 2018; Hage et al., 2013). TEIPP-specific antigens, including ppCT are often self-protein derived, and are processed in the ER directly by a mechanism that involves signal peptidase and signal peptide peptidase before loading onto MHC-I molecules for presentation on the surface of TAP-deficient cells (Hage et al., 2013).

The ability of TEIPP-specific $CD8^+$ T cells to selectively target other TAP-defective cancer types has been demonstrated in colon carcinoma, lymphoma, melanoma, and renal cell carcinoma (Marijt et al., 2019b). It has been hypothesized that TEIPP peptides are only presented by TAP-defective cells because under normal circumstances where functional TAP is intact, TEIPP peptides are outcompeted by the more abundantly available, proteasome-derived peptides to bind MHC-I molecules, or because TEIPP peptides form weaker complexes with MHC-I molecules compared with those generated canonically (Marijt et al., 2019a). Additionally, TEIPP peptide presentation by MHC-I molecules may be necessary for cancer cells to evade natural killer (NK) cells, since NK cells usually target cells that lack surface MHC-I expression.

Furthermore, recent data in cancer patients treated with immune checkpoint inhibitors report treatment failure due to cancer cells acquiring immune resistance by modulating components of the MHC-I peptide presentation pathway or IFN-γ response pathway, which regulates the expression of MHC-I antigen-presentation machinery, as explained earlier. This significantly impairs $CD8^+$ T cell mediated responses (Burr et al., 2019; Manguso et al., 2017; Pan et al., 2018; Patel et al., 2017; Shin et al., 2017; Zaretsky et al., 2016). As an alternative therapeutic strategy, TEIPP peptides have been proposed for use in vaccinations against cancer in humans to induce a robust $CD8^+$ T cell antitumor response, since these peptide are unmutated and ubiquitously expressed in various types of cancers (Durgeau et al., 2018), and the presence of TEIPP-specific naïve T cells has been reported to be common in many people (Marijt et al., 2018). Additionally, targeting TEIPP with *in vitro* expanded TEIPP-specific $CD8^+$ T cell clones has also been proposed as a therapeutic strategy to prevent primary and metastasized cancer cells from evading immunosurveillance (Chambers et al., 2007; Durgeau et al., 2018; Marijt et al., 2019b).

Targeting TAP by viruses to avoid immunosurveillance

Viruses are obligate intracellular parasites and after infecting host cells, they hijack the replication machinery of infected cells to synthesize viral proteins. MHC class I presentation of peptides from these viral proteins elicits an immune response that clears infected cells,

thus neutralizing the viral infection. However, some viruses have evolved mechanisms to evade immunosurveillance by interfering with the immune system, including targeting components of MHC-I peptide presentation, which in some instances can allow viruses to establish chronic or latent infections in a host. Like cancer cells, viruses evade immune surveillance primarily by targeting the TAP proteins, and this is especially true with the Herpesviridae family of viruses (Verweij et al., 2015). TAP's function can be inhibited by the competitive binding of viral proteins to TAP, thus preventing TAP-dependent peptide translocation into the ER lumen (Verweij et al., 2011). A number of such viral proteins have been reported thus far, with the herpes simplex virus (HSV) protein infected-cell protein (ICP47) being the first reported. Structural studies utilising electron cryo-microscopy techniques have resolved the structure and binding confirmation of ICP47 to human TAP, involving the interaction of 36 residues from TAP and 32 residues from ICP47 (Oldham et al., 2016a). The N-terminal region of ICP47 forms a helical hairpin and binds to the cytosolic peptide binding site of TAP as a high affinity competitor, trapping the protein in an inactive conformation, which limits peptide binding and translocation into the lumen of the ER (Oldham et al., 2016b). HSV infected cells infected had decreased surface expression of MHC-I molecules (Hill et al., 1994), which resulted in the inhibition of antigen presentation to $CD8^+$ T cells and a dampened CTL response (York et al., 1994). Interestingly, there are several reported allotypes of HLA-B whose surface expression is variably impacted in the absence of TAP, yet which still allow for the generation of $CD8^+$ T cell responses through the presentation of peptides derived from membrane, secreted and cytosolic proteins, albeit less efficiently than the TAP-dependent pathway (Del Val et al, 2020; Geng et al., 2018.)

Similar TAP inhibition strategies have been reported in other viruses in the Herpesviridae family, including the UL49.5 homologs in pseudorabies virus (Ambagala et al., 2000) and the bovine herpesvirus-1 UL49.5 protein, which interferes and prevents TAP homo- and hetero-dimerization and may mediate the degradation of TAP subunits (Gopinath et al., 2002; Hall et al., 2007; Hinkley et al., 1998). The human cytomegalovirus US6 glycoprotein prevents ATP binding to TAP, which limits the energy available for peptide translocation (Ahn et al., 1997; Hengel et al., 1997). The NLF2a proteins of Epstein–Barr virus and related viruses act in a similar manner by binding to the ATP- and peptide-binding sites of TAP (Hislop et al., 2007; Horst et al., 2009). Targeting of TAP is less common in viruses outside the Herpesviridae family, but does occur, with an example being CPXV012 protein of cowpox virus, which inserts and situates itself in the ER membrane to inhibit ATP binding to TAP, thereby preventing viral antigen presentation to $CD8^+$ T cells (Alzhanova et al., 2009; Byun et al., 2009; Luteijn et al., 2014). Strikingly, these various viral TAP inhibitors likely evolved independently, as they are structurally distinct yet function similarly (Alzhanova et al., 2009).

Like cancer cells, viruses capable of inhibiting TAP have been shown initiate a TEIPP-specific T cell response. In one study, treatment of mouse colon carcinoma cells with UL49.5 caused downregulation of MHC-I molecules on their surface allowing these cells to escape $CD8^+$ T cells, while presentation of TEIPP was strongly promoted (Hall et al., 2007). These findings were extended to human DCs, where the co-culture of UL49.5 treated DCs with autologous T cells resulted in the generation of a TEIPP-specific T cell response (Lampen et al., 2010). Extraordinarily, the TEIPP-specific $CD8^+$ T cell clones displayed

cross-reactivity against cells expressing other viral TAP-inhibitors, such as ICP47, US6, and BNLF2a (Lampen et al., 2010; Marijt et al., 2019a). These findings indicate that different viral proteins that target TAP function lead to similar TEIPP presentation that can prime and give rise to TEIPP-specific T cell immunity against cancer cells or persistent infections with herpes viruses. Such strategies can be therapeutically exploited to treat cancer or herpes virus-infected patients.

TAP polymorphisms and inherited disorders

Many genes involved in antigen presentation are polymorphic, and the genes that encode TAP1 and TAP2 are no exception. Polymorphisms in TAP genes have been linked to an increased susceptibility to some viral infections, autoimmune and autoinflammatory diseases, and an increased susceptibility for some cancers. Mutations that render TAP dysfunctional can cause bare lymphocyte syndrome (BLS), which can be characterized by low levels of most MHC-I molecules on the surface of all cells in the body. In humans, BLS caused by TAP-deficiency has a heterogeneous presentation. This can range from a lack of symptoms, despite a significant downregulation of HLA class I on the surface of immune cells (De La Salle et al., 2002), to patients who suffer from recurrent bacterial infections of the upper respiratory tract, and to the development of granulomatous, necrotizing lesions on the skin, especially on the extremities of the limbs and face, though other symptoms have been noted as well (Gadola et al., 2000). The underlying genetic cause of TAP deficiency can vary, though a mutation that causes a lack of expression of one of the subunits, like a premature STOP codon or a splice site mutation will prevent a functional TAP heterodimer from forming. This means that peptides can thus not be pumped into a secretory compartment to be presented, which leads to unstable HLA class I and impaired expression on the cell surface (De La Salle et al., 1999; Furukawa et al., 1999; Gadola et al., 2000; Moins-Teisserenc et al., 1999). A lack of HLA class I on the cell surface could explain the expansion of NK cells that occurs in many TAP-deficient patients, but it is also possible that this is a compensatory phenomenon, as γδ T cells are also expanded (Moins-Teisserenc et al., 1999), and both of these cell types can recognize cells that are either infected or undergoing some type of stress without the need for MHC expression on the surface (Lawand et al., 2017; Zitti and Bryceson, 2018).

There are also many less severe phenotypes associated with polymorphisms in TAP genes that do not necessarily completely negate their function, yet can still have deleterious effects on the health of the bearer. TAP polymorphisms have been reported to be associated with an increased risk of developing an atopic or autoimmune disorder, and have been noted in patients with systemic lupus erythematosus (SLE) (Correa et al., 2003), rheumatoid arthritis (RA) (Yu et al., 2004), atopic dermatitis (Kuwata et al., 1994; Lee et al., 2001), coeliac disease (Powis et al., 1993) and hypersensitivity pneumonitis (HP) (Aquino-Galvez et al., 2008), among others. However, in many of these studies, the association is weak (McCluskey et al., 2004), and the increase in susceptibility related to the TAP polymorphisms may actually be an artifact of linkage disequilibrium, as the two TAP genes are in close proximity to HLA class II genes, which are themselves highly polymorphic and associated with many autoimmune diseases (Lee et al., 2001; Van Endert et al., 1994). In the case that a polymorphism in a TAP gene does make a functional contribution to

the increased susceptibility in one of these many conditions, the mechanism by which this could happen has yet to be elucidated. It has been speculated that TAP polymorphisms alter the repertoire of peptides that are presented on the surface of cells, which could increase susceptibility to developing autoimmunity (Correa et al., 2003). In TAP-deficient mice, the peptidome of the spleen is significantly altered, with an enrichment in longer peptides with a lower theoretical affinity for MHC-I molecules, likely derived from ER-resident proteins and proteins involved in immune processes (Lorente et al., 2019).

As discussed above, targeting TAP through either the expression of an inhibitory protein or genetic mutation is a strategy that has been co-opted by viruses and in cancer, respectively. Perhaps unsurprisingly, there are also data to suggest that TAP polymorphisms can increase the risk of developing particular cancers, or of becoming infected with particular viruses. TAP polymorphisms are associated with altered susceptibility for initial infection or the development of chronic infection in HIV (Abitew et al., 2020; Kaslow et al., 1996; Liu et al., 2003), Dengue (Soundravally and Hoti, 2008), and human papillomavirus (HPV) (Vambutas et al., 2004), though there are others. In HIV, TAP polymorphisms can increase susceptibility to HIV infection (Abitew et al., 2020), can influence the period of time between initial infection and the development of AIDS (Kaslow et al., 1996), and can even contribute to resistance to HIV infection all together (Liu et al., 2003). In the case of Dengue, heterozygosity at position 665 in the TAP2 gene was linked to a higher likelihood of developing Dengue hemorrhagic fever (DHF) as a result of infection. DHF is thought to be caused by an immune response of an inappropriate scale, and it was speculated that changes to TAP2 function as a result of polymorphisms could contribute to this (Soundravally and Hoti, 2008). As with autoimmune and atopic disorders, to date, no mechanism has been found that can explain the changes to susceptibility to viruses that are linked to polymorphisms in the TAP genes.

As with viruses, polymorphisms in the TAP genes have been found to alter one’s risk of developing cancer (Yamauchi et al., 2014), including cancers that are known to occur as a result of HPV infection (Natter et al., 2016; Zou et al., 2015). Given the numerous correlations between TAP polymorphisms and autoimmunity/atopy, susceptibility to viral infection and progression of chronic viral infection, and the development of cancer, it is surprising that to date, no studies have looked into a potential mechanism by which TAP polymorphisms can alter the immune response. Earlier, it was discussed how a downregulation of TAP expression in cancer can change the repertoire of peptides on the cell surface so drastically as to allow for targeting of cancerous cells by $CD8^+$ T cells while healthy cells are ignored (Marijt et al., 2018; Van Hall et al., 2006). In the case of autoimmune diseases, TAP polymorphisms could alter the stability of TAP such that it is less functional, meaning more ER-derived, self-peptides reach the cell surface, which could lead to a breach of tolerance. The opposite could be true in cases of HIV infection where TAP polymorphism reduces the risk of initial infection or slows infection progression (Kaslow et al., 1996; Liu et al., 2003), where in this case, polymorphisms could allow for more immunogenic peptides to be presented, thus protecting patients. Until mechanistic studies are undertaken, the underlying causes of altered susceptibility to all of these diseases that correlate with TAP polymorphisms will remain speculative.

Future Outlooks

It did not take long after the proposed existence of a peptide pump involved in antigen-presentation for TAP to be discovered, and for its role in direct antigen-presentation and in the cytosolic pathway of cross-presentation to be discovered. We now appreciate that targeting TAP expression is a survival strategy that has been co-opted by both viruses and cancer, demonstrating just how crucial functional TAP is to prime and sustain a $CD8^+$ T cell response. We also understand that loss of TAP results in mobilization of a noncanonical pathway of cross-presentation that bypasses regulation by pattern recognition receptors such as Toll-like receptors, which favor the presentation of microbial antigens during infection associated T cell costimulatory signals. The loss of regulation of antigen presentation during infection or inflammation poses a risk of presenting self-antigens within a T cell costimulatory context. Loss of TAP also leads to the presentation of a unique repertoire of peptides that prime specific CD8 T cells. Despite our understanding of TAP's function and mechanism, many questions remain. Can targeting TAP be developed into an immunotherapy that benefits patients with cancer, perhaps without affecting healthy tissue? Do polymorphisms of the TAP genes that have been associated with an increased risk of developing atopy, autoimmunity, or cancer, or which alter one's susceptibility to viral infection, affect the cross-presentation of some antigens, which could explain these correlations? Understanding how TAP is needed for the cross-presentation of some antigens, but not others, could also have implications for vaccine development. These questions demonstrate the need to continue this three-decade long study of TAP to understand fully how this transporter participates in the development of a robust $CD8^+$ T cell response.

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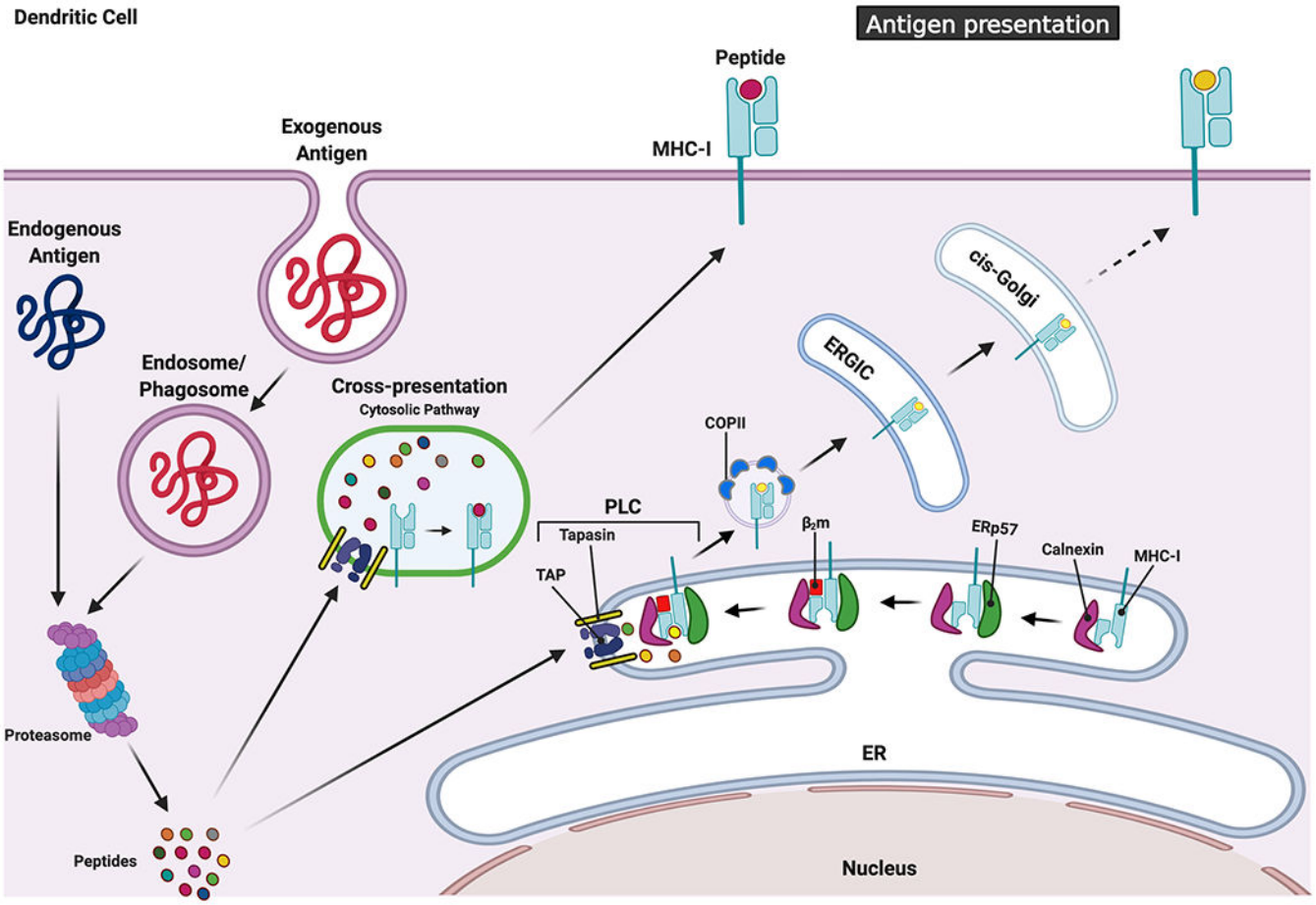

Figure 1 /. An overview of MHC-I antigen-presentation and the cytosolic pathway of cross-presentation in DCs.

Antigen that is either endogenously expressed in the cytosol or that is internalized by an APC and gains access to the cytosol is marked for degradation by ubiquitin ligases (not pictured), then broken down into small 8-10 amino acid long peptides by the proteasome (A.L. Goldberg, 2007). Those peptides are likely passed through a series of cellular chaperones, including hsp90 and hsp70, as discussed in the text (not pictured) before reaching TAP, which then translocates the peptides into the ER for classical MHC-I presentation, or into an endosome/phagosome for cross-presentation (Callahan et al., 2008). There, the peptides are further trimmed by ERAAP in the ER or by IRAP if in a cross-presenting endosome/phagosome (J Magarian Blander, 2018; Saveanu et al., 2009). Following trimming, a peptide of sufficient affinity and the correct size can be loaded onto MHC-I molecules. In the ER, for classical presentation, the source of the MHC-I molecules is the ER itself, while during cross-presentation, the main source is either the plasma membrane or an intracellular network of interconnected vesicles collectively called the ERC, which is marked by Rab11a and is stocked with MHC-I molecules by a poorly understood mechanism (Nair-Gupta et al., 2014). The peptide:MHC-I complex exits the ER via COP-II coated transport vesicles, and then passes through the ERGIC and the cis-Golgi, where it undergoes quality control to ensure proper folding before reaching the cell surface (J. Magarian Blander, 2018).

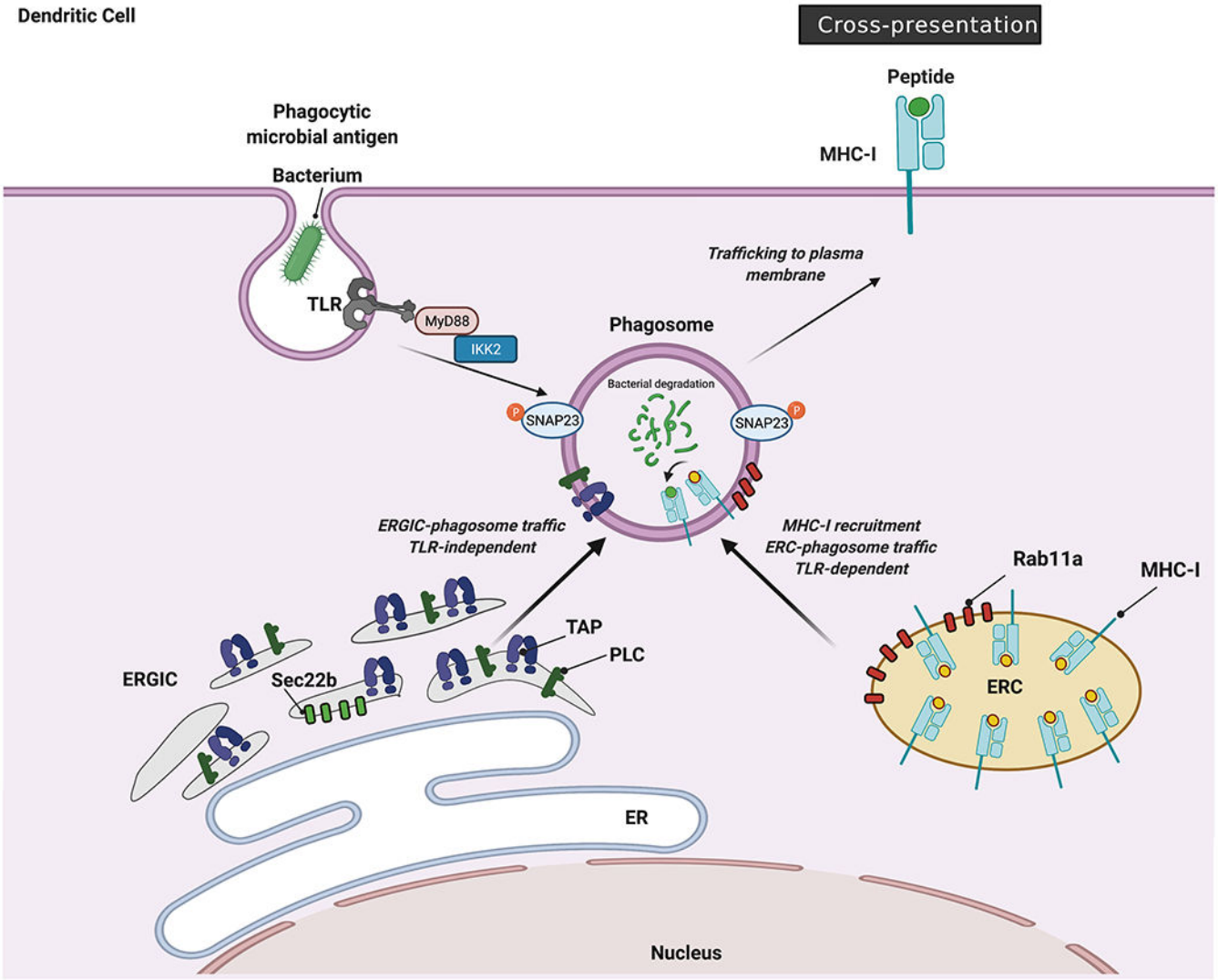

Figure 2 /. Intracellular trafficking of MHC-I and the peptide-loading complex in DCs

Cross-presentation occurs in phagosome/endosomes facilitated by delivery of the required machinery to the vesicle containing the internalized antigen (J Magarian Blander, 2018). TAP and other components of the peptide-loading complex (PLC) are constitutively delivered to the endosome/phagosome when the ERGIC SNARE protein Sec22b interacts with syntaxin-4, a plasma membrane/phagosome SNARE to orchestrate vesicular fusion (Cebrian et al., 2011; Nair-Gupta et al., 2014). Conversely, the trafficking of MHC-I is tightly controlled. MHC-I will only traffic from the endosomal recycling compartment (ERC) to the phagosome if the internalized cargo contains TLR ligands (Nair-Gupta et al., 2014). Once a TLR ligand binds its cognate receptor, a MyD88-dependent signaling pathway is initiated that results in the vesicular traffic from the ERC to the phagosome through phosphorylation of SNAP23, a SNARE-pin stabilizing protein on the phagosome (Nair-Gupta et al., 2014).

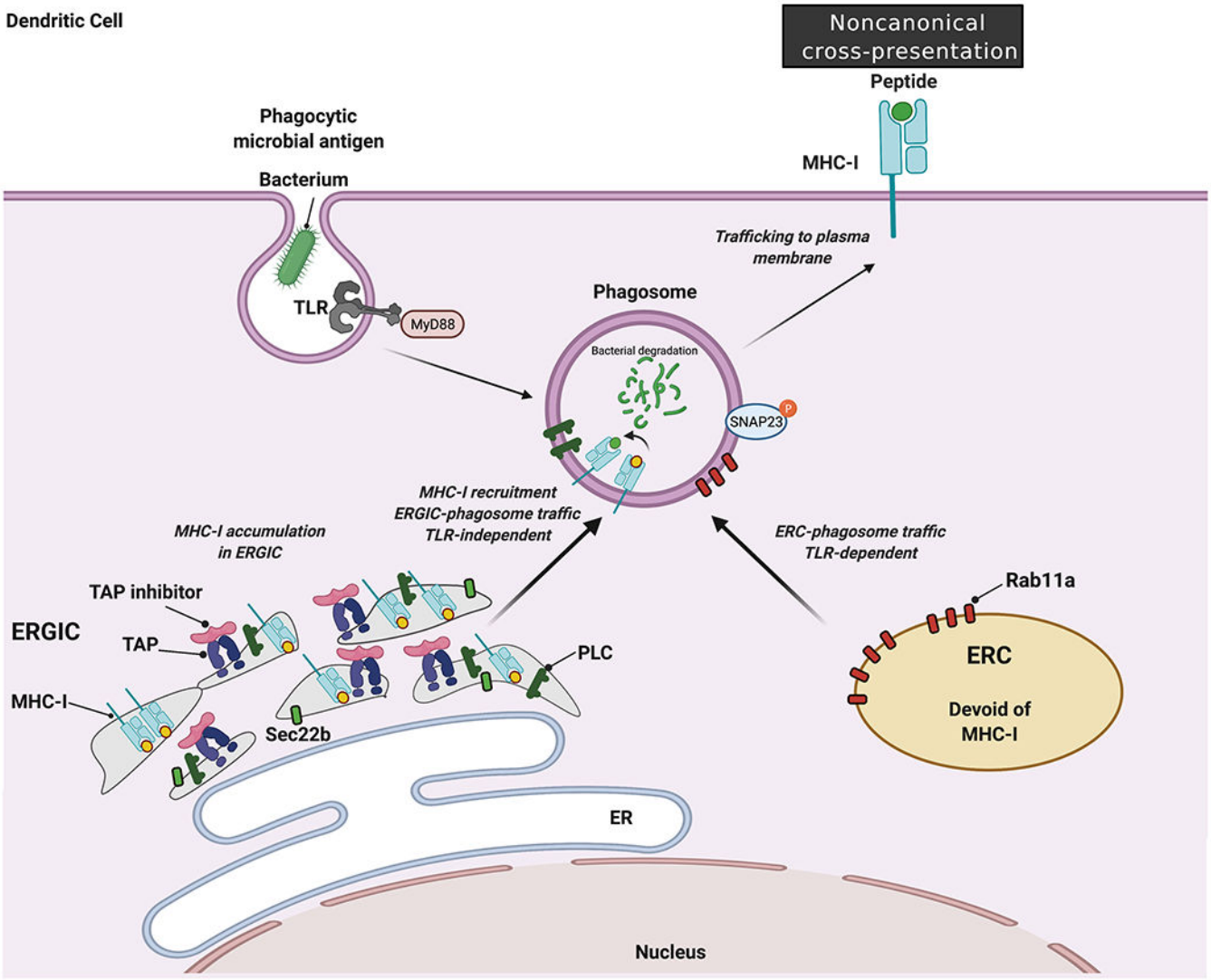

Figure 3 /. TAP blockade in dendritic cells mobilizes a cell-autonomous pathway of noncanonical cross-presentation.

The absence of TAP function creates a paucity of peptides with high-affinity MHC-I binding, and lowers the numbers of properly folded and conformationally stable MHC-I molecules, which fail quality control for export to the plasma membrane, and accumulate within the ERGIC (Blum et al., 2013; Donaldson and Williams, 2009; Raposo et al., 1995). Classical MHC-I presentation is impaired. In the absence of TAP function, the ERC becomes depleted of MHC-I molecules and can thus no longer deliver MHC-I to phagosomes, negatively impacting TLR-regulated cross-presentation (Barbet et al., 2021). Under these conditions of impairment in two major pathways of MHC-I antigen presentation, classical presentation and cross-presentation, DC traffic MHC-I to phagosomes from the ERGIC instead to restore the presentation of exogenously derived peptides in MHC-I (Barbet et al., 2021). Because of the reliance on abnormal traffic of MHC-I, we have named this pathway as non-canonical cross-presentation. Although this pathway appears to represent a back-up for the loss of TAP or potential blockade of this transporter by

pathogens, it escapes regulation by TLRs which do not control Sec22b-mediated traffic from the ERGIC to phagosomes (Barbet et al., 2021).