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Antigen Presentation: Discovery of the Peptide TAP

Luc Van Kaer

This month’s Pillars of Immunology series features four papers published in December 1990, one in Science (1) and three in Nature (2–4), that represented a seminal advance in understanding how CTL sense virus-infected cells. CTL eliminate virus-infected cells by recognizing viral protein fragments displayed on the surface of the infected cells by MHC class I molecules. It was known at the time that the antigenic peptides were generated in the cytosol and that these peptides joined up with MHC class I molecules in an early secretory compartment, most likely the endoplasmic reticulum (ER). However, this raised the conundrum of how cytosolic peptides, most of which lacked N-terminal signal sequences, were able to cross the ER membrane. Based on the phenotype of mutant cell lines with defects in Ag presentation and the assembly of class I molecules in the ER (5–7), Alain Townsend proposed the existence of a peptide pump (8). The four papers simultaneously reported on genes within the MHC class II region encoding proteins related to a family of transmembrane transporters. Although none of the papers provided direct evidence that products of these genes were embedded in the ER membrane or capable of transporting peptides, their membership in a family of transporter proteins together with their genetic location within the MHC class II region appeared to be too much of a coincidence to suggest anything but a peptide transporter function. Discovery of these transporter proteins, now known as transporter associated with Ag processing (TAP1) and TAP2, not only provided an elegant explanation for the mechanism by which cytosolic peptides meet up with MHC class I molecules but also opened up multiple new areas of investigation and discovery.

The simultaneous publication of these four papers clearly reflected the importance of the problem and the pace of research within the field at the time. Although the central message of the four papers was similar, the strategy used by each of the four groups to come upon the new transporter genes was quite different. John Monaco’s group was in pursuit of genes controlling Ag processing (TAP1) and TAP2, not only provided an elegant explanation for the mechanism by which cytosolic peptides meet up with MHC class I molecules but also opened up multiple new areas of investigation and discovery.

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2 Abbreviations used in this paper: ER, endoplasmic reticulum; cim, class I modification locus; LMP, low molecular weight polypeptide; TAP, transporter associated with antigen processing.

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demonstrated a critical role of the TAP pathway for class I-restricted Ag presentation in vivo (14). Finally, direct evidence for peptide transport was obtained by developing in vitro peptide transport assays (13, 15).

Discovery of the peptide transporter opened up numerous new areas of investigation. First, analysis of expressed genes in the vicinity of the tap genes revealed the location of two of the lmp genes (lmp2 and lmp7), which were subsequently shown to encode subunits of the proteasome, the main protease complex responsible for generating class I-binding peptides in the cytosol (12, 16). Further scrutiny of this region of the MHC also revealed genes with similarity to MHC class II molecules, leading to the discovery of the class II peptide exchange factor DM and its regulatory factor DO (17). Second, coimmunoprecipitation experiments revealed interactions between TAP and peptide-receptive MHC class I molecules. This finding, in conjunction with mutant cell line studies, led to identification of the TAP-associated glycoprotein (tapasin), which is encoded at the centromeric end of the MHC (18). It is now well-recognized that tapasin is critical in assembling the MHC class I peptide-loading complex, which includes TAP, tapasin, MHC class I, the chaperone calreticulin, and the thiol oxidoreductase ERP57 (18, 19). Third, peptide translocation experiments revealed that TAP has a preference for 8- to 16-aa-long peptides with hydrophobic C-terminal residues in mouse or with hydrophobic or basic C-terminal residues in human (13, 15). This preference for peptide transport fit well with the specificity of the proteasome and with the prediction of MHC class I molecules for peptides with hydrophobic (mouse and human) or basic (human) C-terminal residues, but it was inconsistent with the preference of MHC class I molecules to bind 8- to 10-aa-long peptides. These findings, together with studies demonstrating peptidase activity in the ER, eventually resulted in the identification of aminopeptidases (ERAP1 and ERAP2) that trim peptides in the ER to the optimal length for binding with MHC class I (20). Fourth, because the tap genes were located within the MHC, a locus with extensive polymorphism, numerous studies have investigated the possibility that TAP polymorphisms might influence immune responsiveness and disease (15). Although several human tap alleles have been identified, convincing evidence for functional polymorphisms is still lacking. However, it was a functional polymorphism in TAP2 that led to the discovery of TAP in the rat. The tap2b allele (cim3) confers the rat transporter with a preference for peptides with hydrophobic C termini (like mouse TAP), whereas the tap2a allele (cim4) confers a preference for peptides with hydrophobic or basic C termini (like human TAP) (21). Fifth, a direct linkage with human disease was revealed by showing that a subset of patients with bare lymphocyte syndrome had defects in tap1 or tap2 (22). Patients with this syndrome, now referred to as bare lymphocyte syndrome type 1, suffer from chronic inflammation of the respiratory tract and necrotizing granulomatous skin lesions. Sixth, several viruses, including herpes simplex virus and human cytomegalovirus, encode proteins that directly bind to TAP and interfere with its transport function, therefore evading CTL recognition (22, 23). Finally, some tumors have found a way to interfere with peptide transport by down-regulating TAP expression, thus evading recognition by class I-restricted CTL (22).

In summary, discovery of the TAP peptide pump provided a simple yet elegant explanation for the delivery of cytosolic viral peptides to ER-resident MHC class I molecules for scrutiny by MHC class I-restricted CTL.

References