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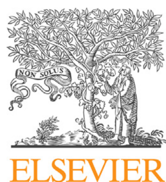

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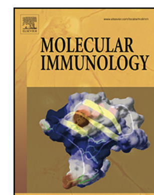

Review

Are ERAD components involved in cross-presentation?

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ABSTRACT

A long unanswered question in the antigen presentation field is how exogenous antigens cross-presented by Major Histocompatibility Complex class I (MHC-I) molecules to CD8+ T cells are translocated into the cytosol. Here we discuss the known mechanisms involved in this process with a focus on the hypothesized role of the machinery that functions in endoplasmic reticulum-associated degradation (ERAD). Other potential mechanisms of antigen entry to the cytosol are also discussed.

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1. Introduction

The majority of MHC-I-associated peptides are derived from proteins synthesized within the cell. However, some antigen presenting cells (APC) can process and present peptides from exogenous antigens on MHC-I in a process termed cross-presentation. This can occur through two main pathways: by endo/lysosomal processing of the antigen and peptide binding to MHC-I molecules within the endocytic pathway, or by the antigen gaining access to the cytosol. The latter process poses an interesting cell biological question: How do antigens enclosed by endosomal or phagosomal membranes gain access to the MHC-I processing machinery localized in the cytosol and endoplasmic reticulum (ER)? Here we will focus solely on the cytosolic pathway of cross-presentation.

2. Overview of the cytosolic cross-presentation pathway

Cross-presentation of antigens internalized by macrophages was originally shown to require proteolysis by cytosolic proteasomes and peptide transport by the Transporter associated with Antigen Processing (TAP) (Kovacsovics-Bankowski and Rock, 1995). This suggested that an antigen originating in a phagosome must somehow escape from it to be presented. Since then many studies have demonstrated that diverse antigens can be cross-presented by this pathway. Surprisingly, twenty years later, we still have a very poor understanding of the process. One obstacle has been the lack of good assays that directly detect the entry of phagosome-derived proteins into the cytosol. CD8+ T cells are exquisitely sensitive and can detect and respond to very few peptides bound to MHC-I, so the downstream consequence of antigen translocation from phagosome to cytosol, namely T cell recognition, is relatively easy to demonstrate. However, it is likely that only a small fraction of the internalized antigen gains access to the cytosol, and discerning that population from the phagosome-localized population presents a significant biochemical challenge. Assays using enzymes such as luciferase or β-lactamase, or apoptosis induced by exogenously supplied cytochrome c, have demonstrated that cells able to cross-present, commonly dendritic cells (DCs) or their transformed derivatives, are efficient in translocating such proteins to the cytosol (Cebrian et al., 2011; Giodini and Cresswell, 2008; Lin et al., 2008), but they have not yet revealed the machinery responsible. In addition, in these assays relatively large amounts of the proteins are required to see a signal, much more than is physiologically required for cross-presentation.

3. A role for ER components in cross-presentation

Several groups have described the delivery of normally ER-localized proteins to phagosomes, providing the original basis for the hypothesis that the mechanisms responsible for ERAD might also be responsible for the delivery of phagosomal antigens to the cytosol (Ackerman et al., 2003; Guermonprez et al., 2003; Houde et al., 2003). Sec61, the complex of proteins that imports proteins into the ER undergoing translation on membrane-associated ribosomes, was previously suggested to deliver misfolded proteins back

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into the cytosol for degradation (Pilon et al., 1997) and it was one of the ER components acquired by early phagosomes (Guermonprez et al., 2003; Houde et al., 2003). In addition, phagosomes were shown to acquire MHC-I and components of the peptide loading complex (PLC), including TAP, and to associate with proteasomes (Ackerman et al., 2003; Guermonprez et al., 2003; Houde et al., 2003). These data led to the attractive model that cytosolic access mediated by the components involved in ERAD, proteasomal processing, TAP transport of proteasomally generated peptides, and MHC-I loading might all occur in a localized environment that could partially restrict the peptide repertoire to that derived from phagosomes. Moreover, delivery of ER proteins to phagosomes is dependent on Sec22b, a SNARE that localizes to the Golgi/ERGIC and can mediate fusion with binding partners at the plasma membrane and phagosomes (Becker et al., 2005; Cebrian et al., 2011; McNew et al., 2000), suggesting that a vesicular fusion mechanism may be responsible for the acquisition of ER proteins by phagosomes.

Whether there is a genuine role for Sec61 in cross-presentation is unclear (see below), but at least one ER-localized multi-protein complex efficiently translocates proteins from the ER to the cytosol. Once secretory proteins are translocated into the ER via Sec61 they require the help of chaperones, oxidoreductases, and the glycosylation machinery to fold properly. A subset of translocated proteins is unable to attain the correct conformation, becomes terminally misfolded, and needs to be eliminated before accumulation results in toxicity. The ERAD machinery identifies the misfolded proteins and translocates them back into the cytosol where they are degraded by the proteasome. At the core of the ERAD membrane complex are E3 ubiquitin ligases. In mammalian cells, the most well studied are Hrd1 and gp78/AMFR, although other ER-localized E3 ligases can function in ERAD (Mehnert et al., 2010). These E3 ligases ubiquitinate the ERAD substrate and, at least for yeast Hrd1p, may also serve as the channel that mediates access to the cytosol (Carvalho et al., 2010; Stein et al., 2014). The ERAD membrane complex also contains accessory factors that can serve as scaffolds to nucleate the complex (SEL1L) (Mueller et al., 2008), recruit the ERAD complex to specific ER domains (HERP) (Leitman et al., 2014), lectins that can bind glycan moieties on misfolded proteins (OS-9, XTP3-B, EDEMs) (Christianson et al., 2008; Hosokawa et al., 2001), and other factors with less well-defined functions such as Derlin-1 (Lilley and Ploegh, 2004; Ye et al., 2004). Once the ERAD machinery has recognized and ubiquitinated a misfolded protein and it has partially entered the cytosol through the translocon, the AAA-ATPase p97 and its two binding partners UFD1/NPL4, bind the substrate and pull it into the cytosol (Ye et al., 2001), where the substrate is deglycosylated by peptide:N-glycanase and degraded by the proteasome. While the factors listed above are required for ERAD of many substrates, it should be noted that individual proteins have different requirements for ERAD factors.

As mentioned above, Sec22b is required for trafficking of ER-derived vesicles to phagosomes. Furthermore, when Sec22b is knocked down using shRNA, there is a decrease in cross-presentation as well as protein translocation into the cytosol, suggesting that ER-derived factors are responsible (Cebrian et al., 2011).

4. Are ERAD components required for cross-presentation?

One group reported that exogenously added ovalbumin (OVA) interacts with p97, the cytosolic component required for complete dislocation of ERAD substrates (Imai et al., 2005). Furthermore, knockdown of p97 using siRNA led to both a decrease in degradation of exogenously added OVA and a decrease in its cross-presentation. Expression of a dominant negative (DN) form of p97 that lacks the ATPase activity also decreases cross-presentation, and addition of recombinant DN p97 to purified phagosomes containing luciferase leads to a decrease in the ATP-dependent release of luciferase from the phagosomes (Ackerman et al., 2006). Subsequently, it was demonstrated that binding of OVA to the mannose receptor (MR) induces polyubiquitination of the receptor, leading to recruitment of p97 to endosomes (Zehner et al., 2011). Not only was p97 recruitment required for cross-presentation of OVA, but also for it to enter the cytosol. Another study examining the cross-presentation by human DC showed that knockdown of p97 using a small interfering RNA (siRNA) led to decreased cross-presentation of a MelanA/MART1 epitope (Menager et al., 2014). These data are consistent with a role for p97 in facilitating the cytosolic access and cross-presentation of several different antigens.

ERAD requires the coordination of many factors for efficient retrotranslocation. Do other ERAD factors besides p97 play a role in cytosolic access of cross-presented antigens? siRNA-mediated knockdown of Derlin-1 did not lead to a decrease in cross-presentation of long peptides by human DC (Menager et al., 2014). In our own unpublished work we have found that shRNA-mediated knockdown of three ERAD components, namely Hrd1, gp78, and HERP, had little effect on cross-presentation by murine DCs of OVA associated with latex beads, nor did expression of a DN form of Derlin-1 (Table 1). Other experiments clearly showed that knockdown of these components substantially impacted ERAD of glycosylated fluorescent protein derivatives (Grotzke et al., 2013). Together, the data argue that the major components of the defined ERAD membrane complexes are not involved in retrotranslocation of cross-presented antigens from phagosomes.

The Sec61 channel, which co-translationally translocates proteins into the ER, has been proposed to be the translocon for cross-presentation. Sec61α and β have been shown to associate with exogenously added soluble OVA (Imai et al., 2005). Knockdown of Sec61α or β in a DC-like cell line led to decreased degradation of OVA as well as decreased cross-presentation (Imai et al., 2005). Treatment of APCs with exotoxin A (ExoA) from *Pseudomonas aeruginosa*, a toxin that, in a cell free system, inhibits the export of small peptides from ER vesicles through potential interactions with Sec61 (Koopmann et al., 2000), led to a decrease

Table 1
Involvement of ERAD factors in cross-presentation.

Gene	ERAD role	Role in cross-presentation?	References
Hrd1	Transmembrane E3 ligase, translocation?	No	Grotzke (unpublished)
gp78	Transmembrane E3 ligase	No	Grotzke (unpublished)
CHIP	Cytoplasmic/nuclear E3 ligase	Yes	Imai et al. (2005)
HERP	Recruitment of ERAD membrane complex to the ER-derived quality control compartment	No	Grotzke (unpublished)
p97	Dislocation of ERAD substrates	Yes	Ackerman et al. (2006), Imai et al. (2005), Menager et al. (2014), Zehner et al. (2011)
Derlin-1	Transmembrane protein, poorly defined function	No	Menager et al. (2014), Grotzke (unpublished)
Sec61	Tranlocation into the ER, retrotranslocation out?	?	Ackerman et al. (2006), Imai et al. (2005), Menager et al. (2014)

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