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Regulation of Antigen Cross-Presentation in Immunity: A Comprehensive Review

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Abstract

Antigen cross-presentation is a specialized process by which dendritic cells (DCs) digest and present external antigens on MHC-I molecules, enabling the activation of CD8+ cytotoxic T lymphocytes (CTLs) essential for immune defense against infections, malignancies, and intracellular pathogens. Unlike the traditional MHC-I pathway for endogenous antigens, cross-presentation allows recognition of external threats. This complex mechanism involves antigen uptake, processing, trafficking, and MHC-I loading through cytosolic and vacuolar pathways, with scavenger and pattern recognition receptors (PRRs) playing key roles. Cytokines and inflammatory signals also influence DC function and cross-presentation efficiency. Understanding these regulatory mechanisms is crucial for advancing immunotherapies and vaccines to improve immune response and treatment outcomes.

Keywords: Antigen, Cross-presentation, MHC-I, Dendritic cells, CD8$^+$ T cell

1. Introduction

The cross-presentation pathway is different from the conventional procedure because it does not follow the usual way in which MHC-I molecules present peptides from endogenous sources within the cell. Cross-presentation, on the other hand, alters this system so that it can display peptides from extracellular proteins, such as those from pathogens, dead cells, or tumors [1–4]. This divergence is significant because it allows the immune system to activate CD8+ T cells against threats that may not directly infect antigen-presenting cells (APCs) themselves. As a result, antigen cross-presentation is an essential and unique part of the immune system's surveillance and defensive mechanisms [1,5–7]

There are significant biological challenges that arise from the fact that the compartments where internalized antigens are broken down and the endoplasmic reticulum (ER), where MHC-I molecules are loaded, are located in different places[8,9]. As a result, cross-presentation requires the creation of specialized cellular adaptations to coordinate the processes of transport, degradation, and peptide loading [6]. This work investigates these issues and highlights new findings about the ways in which a number of biological mechanisms contribute to effective cross-presentation[10–12].

2. Cellular Pathways That Are Involved in Cross-Presentation

Antigen cross-presentation necessitates a highly coordinated interaction between intracellular compartments that are responsible for the uptake, processing, and peptide loading of antigens onto MHC-I molecules. The endocytic vesicles, phagosomes, endoplasmic reticulum (ER), and Golgi apparatus are the main compartments that are involved in cross-presentation. The endocytic vesicles and phagosomes are the first places where

antigens are broken down. The endoplasmic reticulum and Golgi apparatus are typically involved in the production and loading of MHC-I. These compartments collectively regulate antigen trafficking and processing to ensure efficient presentation to CD8+ T cells, a process that is particularly important for initiating immune responses against pathogens, tumors, and apoptotic cells[5,12].

Cross-presentation is facilitated by two different antigen-processing processes: the cytosolic athway and the vacuolar pathway. Each of these pathways provides a different mechanism for antigen breakdown and peptide loading onto MHC-I molecules. The presence of these two pathways highlights the immune system's ability to adapt to various types of antigens and improve T cell activation.

2a. Cytosolic Pathway or TAP dependent Pathway

The cytosolic pathway, also known as the proteasome-dependent pathway, involves the transfer of endocytosed antigens from the phagosomes to the cytosol, where they undergo proteasomal breakdown. This pathway is quite similar to the traditional endogenous antigen presentation method. In this process, intracellular proteins are ubiquitinated and broken down by the proteasome. After that, they are transported back into the endoplasmic reticulum (ER) for loading onto MHC-I. On the other hand, foreign antigens must first escape from vesicular compartments in order to access the cytosol in the event of cross-presentation [13].

This escape is made possible by mechanisms that include the rupture of phagosomal or endosomal membranes or by active translocation systems, such as Sec61, which has been discovered as a molecular channel responsible for transferring proteins across membranes. Antigens are broken down by the proteasome, which is a multi-protein complex that is responsible for breaking down polypeptides into smaller peptide fragments. This process occurs once the antigens are in the cytosol [1].

These antigen-derived peptides must be carried back into endosomal or phagosomal compartments after they have been degraded. Once they are in these compartments, they will bind to MHC-I molecules. The transporter associated with antigen processing (TAP) is a major molecular participant in antigen presentation, and it is responsible for mediating this transport. In order for the produced peptides to reach the relevant compartments for MHC-I loading, TAP-dependent peptide transport is necessary. After entering the vesicular lumen, the peptides are further trimmed by ER-associated peptidases, such as ERAP1 and ERAP2. These enzymes refine the peptide fragments to the ideal size for MHC-I binding [14,15].

The cytosolic pathway is a highly selective and efficient way to generate peptides, which allows for the presentation of a wide variety of antigenic epitopes. This pathway is especially important in cases of viral infections and cancer, when it is necessary to process antigenic proteins with a high precision to ensure an effective cytotoxic T cell response. On the other hand, this route also necessitates strict management because inappropriate antigen escape or excessive breakdown could result in ineffective peptide loading or immunological tolerance rather than activation [16].

2b. Vacuolar Pathway or TAP Independent Pathway

The vacuolar pathway, which is also referred to as the proteasome-independent method or the endosome-based pathway, is an alternative method of doing cross-presentation. In this process, antigen processing takes place solely within endosomal or phagosomal compartments, and it does not require translocation into the cytosol. This pathway is particularly useful for processing antigens that are resistant to proteasomal degradation or that require distinct processing conditions to be optimally presented on MHC-I molecules [16,17].

The vacuolar pathway keeps the antigens inside late endosomes or phagosomes, where they are broken down by lysosomal proteases like cathepsins S, B, and L. This is different from the cytosolic pathway, where the antigens need to exit the vesicles. These proteases slowly break down antigens into peptide fragments, which are then loaded directly onto MHC-I molecules in the same compartment [18].

Phagosomal pH regulation is one of the most important regulatory mechanisms in this pathway. Vacuolar ATPases (v-ATPases) are responsible for controlling the acidity of phagosomes. They do this by aggressively pumping protons into the vesicles, which helps to create the best possible environment for the breakdown of antigens. However, if the acidity is too high, it might lead to excessive degradation of antigens, which decreases the chances of successful cross-presentation. NADPH oxidase (NOX2) produces reactive oxygen species

(ROS) to counteract this. These ROS help to regulate the pH of the phagosome by keeping it from becoming too acidic. This controlled balance guarantees that antigens are digested enough without being fully broken down, which enables efficient peptide loading onto MHCI molecules [19].

The vacuolar route is also characterized by its dependence on vesicle-to-vesicle fusion events. Antigen-containing vesicles combine with MHC-I-loaded compartments, which allows for the direct transfer of processed peptides to the MHC-I groove. SNARE proteins, such as Sec22b, help in this process. They have been demonstrated to help move MHC-I molecules to phagosomal compartments. This vesicular fusion method enables MHC-I molecules to obtain antigenic peptides without the need for cytosolic transport, making it a more efficient alternative to the TAP-dependent cytosolic pathway [18,20].

The vacuolar route is especially significant in dendritic cells (DCs) that are specialized for antigen presentation, such as CD8α+ DCs, which are very effective at processing external antigens. It is also believed to be advantageous in situations when TAP is absent or downregulated, such as during some infections or in tumor microenvironments that try to avoid immune recognition by reducing TAP expression [21].

Both routes perform complementary functions in cross-presentation, allowing DCs to respond to different types of antigens under varying situations. The cytosolic approach guarantees the accurate synthesis of peptides through proteasomal processing, while the vacuolar pathway offers a different method that enables antigen processing to take place solely within endocytic compartments. The pathway that is chosen is determined by a number of different parameters, such as the type of antigen, the subset of dendritic cells that are engaged, and the inflammatory or immunological background [22].

For instance, the cytosolic pathway is preferred by certain viral proteins and tumor antigens that require fine-tuned proteasomal cleavage, while the vacuolar pathway is preferred by bacterial and apoptotic cell-derived antigens, which may not require such extensive processing [23]. Furthermore, innate immunological signals, such as the activation of Toll-like receptors (TLRs), can affect the dominance of one pathway over another. This adds to the complexity and adaptability of antigen cross-presentation processes [24].

3. Endosomal and Phagosomal Trafficking in Antigen Processing

Endocytic vesicles and phagosomes are the first places where internalized antigens are broken down. These compartments are diverse and regulated through various vesicular trafficking pathways that help maintain the integrity of antigens while allowing for degradation and processing [25].

3a. Early and Late Endosomes

Antigens that have been internalized are sent to early endosomes and then eventually to late endosomes or phagosomes, where they come into contact with enzymes that start the process of degradation [17,26,27]. This procedure is essential for producing the peptide fragments that are required for MHC-I binding. Rab GTPases and other important regulators assist in the coordination of endosomal maturation and fusion processes, which are essential for the transportation of antigens to the correct locations within the cell [24].

3b. Endoplasmic Reticulum (ER)-to-Phagosome Trafficking

The ER is the location where MHC-I molecules are typically loaded with peptides from endogenous sources. During cross-presentation, however, components of the ER, including the transporter associated with antigen processing (TAP) and other molecular chaperones, are transported to the phagosomes. The connection between the ER and the phagosome, which is made possible by SNARE proteins such as Sec22b, allows MHC-I molecules to load peptides into the phagosomes without having to go back to the ER [2,3,25].

3c. The Function of Vesicle Recycling in Antigen Presentation

Endosomes that are recycled help with cross-presentation by moving MHC-I molecules back to the surface of the cell after they have taken in peptide antigens. Proteins like Rab11a help recycle MHC-I, which guarantees that it is always available for presentation. This increases the cell's ability to stimulate CD8+ T cells [28].

4. Regulation by Toll-like receptors (TLRs) and immune receptors

The receptors on the surface of dendritic cells (DCs), such as Toll-like receptors (TLRs), help to regulate the ability of DCs to cross-present efficiently. TLRs recognize pathogenassociated molecular patterns (PAMPs) and play an important role in modulating antigen processing [20]. TLR engagement can greatly improve cross-presentation by changing the pH of phagosomes, adjusting degradation rates, and affecting peptide loading.

4a. TLR-Mediated Vesicular Modulation

TLRs on DCs activate pathways that can change the way vesicles move, especially with regard to phagosomal acidification. For instance, reactive oxygen species (ROS) that are produced by NADPH oxidase work against the acidification that is caused by the v-ATPase. This results in a pH that is more neutral, which is better for preserving antigens than for quickly breaking them down. This balance is crucial because too much acidification can destroy antigens before they are processed, while too little acidification can impair peptide generation [24].

4b. Innate Receptor-Mediated Targeting of Antigen Sources

Receptors like CLEC9A, mannose receptors, and CD91 are able to identify specific motifs on pathogens or dead cells, which allows them to direct antigens toward cross-presentation pathways. Every receptor-mediated pathway has different results, directing antigens to certain intracellular compartments where they can be processed effectively for cross-presentation. This specificity is especially relevant in cancer immunotherapy, where directing tumor antigens to DCs is a potential strategy for activating robust T-cell responses [29,30].

5. Molecular Challenges and Quality Control in Cross-Presentation

Cross-presentation poses molecular challenges. Quality control processes guarantee that only stable and high-affinity peptide-MHC-I complexes are able to reach the cell surface:

5a. Molecular Chaperones in MHC-I Assembly

MHC-I molecules are folded and stabilized by chaperones like calnexin, calreticulin, and ERp57, which help to stabilize the peptide-binding groove. This stabilization is essential because it guarantees that only peptides with the best affinity are presented, which increases the potential for T cell activation [31].

5b. ER-Golgi Intermediate Compartment (ERGIC)

The ERGIC plays an intermediary role in the trafficking of MHC-I molecules from the ER to phagosomes. Research indicates that ERGIC components, including TAP and Sec22b, are transported to phagosomes that contain microbial or pathogenic antigens. Once there, they assist in the final stages of antigen processing and presentation [31,32].

6. The Importance of Cross-Presentation in Immunotherapy and Vaccine Development

Understanding cross-presentation is crucial for creating effective vaccines and immunotherapies, as it plays a pivotal role in generating strong and targeted immune responses against intracellular pathogens, tumors, and other disease-related antigens. Unlike the classical MHC-I pathway, which primarily presents endogenous antigens, cross-presentation allows dendritic cells (DCs) to process and present external antigens on MHC-I molecules, effectively stimulating CD8+ cytotoxic T lymphocytes (CTLs). This mechanism is essential for eliminating infected or malignant cells that otherwise evade immune detection.

6a. Vaccines for Intracellular Pathogens and Tumors

Cross-presentation is essential for the development of T cell responses against intracellular pathogens and tumor cells, which frequently avoid the body's normal immune responses. Vaccines that improve DC cross-presentation may enhance the immune response against these difficult targets [33,34].

6b. Targeting Receptors to Improve Cross-Presentation

Researchers can increase the effectiveness of vaccines by selectively activating receptors that favor cross-presentation. For instance, mannose receptor-targeted vaccines that deliver antigens directly to early endosomes have shown promise in enhancing immune responses due to efficient antigen processing and peptide loading on MHC-I [35].

6c. Checkpoint Inhibition and Cross-Presentation

Cross-presentation by DCs plays a role in the efficacy of checkpoint blockade therapies, which seek to "release the brakes" on the immune system, allowing T cells to target tumors more effectively. As a result, improving cross-presentation can be used in conjunction with checkpoint inhibitors, which can lead to a more powerful response against tumors[36].

7. Emerging Challenges and Future Directions

Some of the new issues that have arisen in the effort to completely understand and optimize cross-presentation include clarifying subcellular pathways in distinct DC subtypes, enhancing the transport and preservation of antigens, and using cross-presentation in autoimmune and tolerance. Different subsets of dendritic cells (DCs) have different abilities to deliver antigens to T cells. Understanding these variances could improve targeted therapy for cancer and infectious disorders. Furthermore, the use of nanoparticles or conjugated ligands to improve the stability and transport of antigens may also improve the absorption and processing of antigens. In addition, cross-presentation has two functions: it activates CD8+ T cells and helps the body to tolerate its own immune system. This shows that additional research is needed to understand how cross-presentation is regulated so that treatments for autoimmune diseases can be developed [37,38].

8. Conclusion

Antigen cross-presentation by DCs represents a sophisticated system for mobilizing cytotoxic T cell responses against pathogens and tumors. DCs are responsible for the processing and presentation of extracellular antigens in a way that maximizes the immune system's vigilance. They accomplish this through complex trafficking and molecular signaling pathways. The intricate processes that are responsible for cross-presentation offer important information about the way the immune system reacts to complicated dangers and create a number of potential treatment options. Future research and clinical applications can improve immune responses, increase the effectiveness of vaccines, and develop targeted immunotherapies that more effectively utilize the body's own defense mechanisms to fight infections and cancer by taking advantage of the complexities of cross-presentation.

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