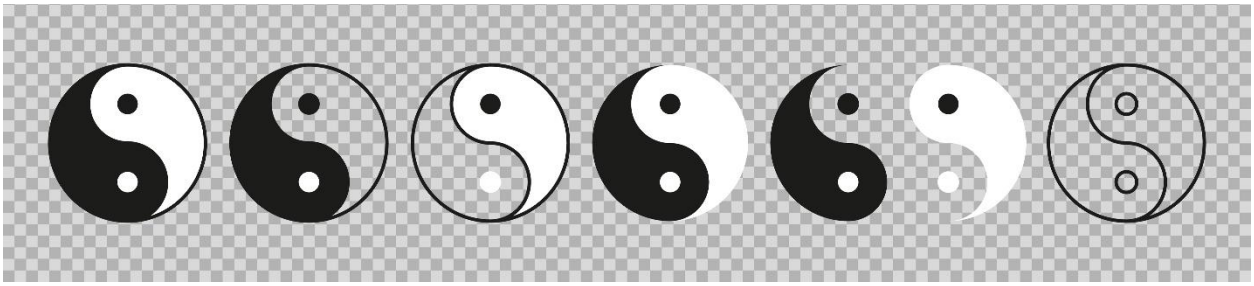
MarinBio Blog

The Yin and Yang of Targeting Antigen Processing for Autoimmune Disease and Cancer



Antigen processing sits at a biological crossroads where the immune system decides whether to tolerate or attack. In autoimmune disease, this pathway becomes overzealous, presenting self-antigens that fuel harmful immune responses. Here, the therapeutic “Yin” aims to quiet the system, reducing antigen generation, trimming, or loading so that autoreactive T cells are starved of the signals that drive inflammation. By damping MHC presentation, the immune system is gently steered back toward tolerance.

Cancer represents the opposite pole, the “Yang”—where tumors often hide by limiting antigen processing and MHC display. Instead of suppression, therapy seeks amplification: boosting peptide generation, enhancing MHC loading, and increasing neoantigen visibility so cytotoxic T cells can recognize and eliminate malignant cells. In this context, upregulating antigen presentation transforms immune-cold tumors into immune-visible targets.

Together, these opposing strategies highlight the dual nature of antigen processing as a therapeutic opportunity. Whether dialing the system down in autoimmunity or turning it up in cancer, manipulating this pathway reveals the balance regulating immune control.

Antigen Presentation in Human Health and Disease

Beyond its essential role in protecting against pathogens, antigen presentation also contributes to the development of autoimmune diseases when dysregulated. Aberrant presentation of self-antigens can trigger immune responses, leading to conditions such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis, where the immune system mistakenly attacks healthy tissues. In contrast, inadequate antigen presentation or defects in MHC molecules can impair immune surveillance, increasing susceptibility to cancer. Understanding the pathways and regulation of antigen presentation is therefore critical not only for elucidating mechanisms of

immune defense but also for developing therapies that modulate immune responses in autoimmune diseases, infectious diseases, and cancer immunotherapy.

Mechanisms of Antigen Presentation

MHC Class I Antigens. (MHC Class I is expressed by almost ALL nucleated cells).
Source of antigens: Intracellular proteins, typically from viruses, intracellular bacteria, or abnormal/mutated self-proteins
-Processing pathway: Cytosolic (endogenous pathway)

1. Protein degradation: Cytosolic proteins are degraded by the proteasome into short peptides (8–10 amino acids).
2. Peptide transport: Peptides are transported into the endoplasmic reticulum (ER) by TAP (Transporter associated with Antigen Processing).
3. Loading: Peptides bind to newly synthesized MHC Class I molecules in the ER.
4. Transport to surface: The peptide-MHC I complex is transported via the Golgi to the cell surface.

-Recognition: Presented peptides are recognized by $CD8^+$ cytotoxic T lymphocytes (CTLs).
-Function: Alerts the immune system to intracellular infections or cancerous transformations.

MHC Class II Antigens. (MHC Class II is expressed by specialized antigen-presenting cells).
Source of antigens: Extracellular proteins, typically from phagocytosed pathogens.
-Processing pathway: Endocytic (exogenous pathway)

1. Endocytosis/phagocytosis: Antigens are internalized into endosomes/phagosomes.
2. Protein degradation: Proteins are degraded into peptides by acidic proteases in Endo lysosomal compartments.
3. MHC Class II synthesis: MHC II molecules are synthesized in the ER, where they are bound by invariant chain (Ii) to prevent premature peptide binding.
4. Transport to endosome: MHC II + Ii complex is transported to the peptide-containing endosome, where the invariant chain is degraded, leaving a small fragment (CLIP) in the binding groove.
5. Peptide loading: HLA-DM facilitates replacement of CLIP with antigenic peptides.
6. Transport to surface: The peptide-MHC II complex moves to the cell surface.

-Recognition: Presented peptides are recognized by $CD4^+$ helper T cells.
-Function: Activates helper T cells to stimulate B cells, macrophages, and other immune responses.

Role of Antigen Processing in Autoimmune and Cancer Development and Progression

Antigen processing plays a significant role in both autoimmune diseases and cancer development/progression, but the mechanisms differ depending on the context.
Although both MHC class I and class II pathways contribute to disease, class II–restricted presentation often plays a dominant role in driving autoimmunity, whereas class I–restricted antigen processing and presentation are typically more critical for tumor recognition, immune surveillance, and cancer immune evasion.

Table 1. Key differences at a glance

Feature	MHC Class I	MHC Class II
Source of antigen	Endogenous (intracellular)	Exogenous (extracellular)
Peptide length	8–10 amino acids	13–25 amino acids
Presenting cells	Almost all nucleated cells	Professional APCs (DCs, macrophages, B cells)
Recognized by	$CD8^+$ T cells	$CD4^+$ T cells
Processing compartment	Cytosol to ER	Endosome/lysosome

Autoimmune Disease

In autoimmune disease, antigen processing refers to the intracellular degradation of proteins into peptides that are subsequently loaded onto MHC molecules and presented to T cells. Under normal conditions, processing of self-proteins leads either to immunological ignorance or the induction of tolerance. In autoimmune pathology, however, this process becomes dysregulated, enabling the generation and display of peptides that activate autoreactive T cells primarily through MHC class II pathways. Alterations in antigen processing machinery, including mutations or dysregulation within the proteasome, lysosomal enzymes, or autophagy pathways, can shift the peptide repertoire toward enhanced or cryptic epitopes capable of breaking immune tolerance. Such changes are implicated in disorders such as type 1 diabetes, multiple sclerosis, and rheumatoid arthritis. Clinically, these insights have guided therapeutic strategies aimed at modulating antigen presentation or downstream T cell activation, including agents such as CTLA-4–Ig or MHC-targeted inhibitors that suppress autoimmune responses by dampening or reshaping antigen display.

Cancer

In cancer, antigen processing also plays a decisive role but in fundamentally different ways. Tumor cells frequently evade immune surveillance by altering components of their antigen processing pathways, thereby reducing the presentation of tumor-associated antigens on MHC molecules. Common mechanisms include the downregulation of proteasome subunits, reduced expression of TAP transporters, or loss of MHC class I itself, all of which diminish recognition by cytotoxic T lymphocytes. Conversely, the same processing machinery is responsible for generating neoantigens from mutated proteins, key features that allow T cells to specifically recognize and destroy cancer cells. Clinically, therapeutic strategies that modulate antigen processing, including proteasome inhibitors or agents that enhance TAP activity, are being explored to improve the efficacy of immunotherapies by restoring or amplifying tumor antigen visibility.

Summary

- In autoimmunity: class II antigen processing/presentation is usually the primary driver of disease initiation and progression, with class I modifying severity through cytotoxic and regulatory circuits.
- In cancer: class I antigen processing/presentation is usually more critical for direct tumor control and immune escape, while class II (on APCs and some tumors) is key for sustaining and optimizing anti-tumor immunity, especially under checkpoint blockade.

Drugs That Modify Antigen Presentation: Major Approaches & Examples

See tables 2 and 3 bellow. Antigen presentation is a central determinant of immune recognition, and recent drug development has increasingly focused on modulating this pathway to enhance therapeutic outcomes in autoimmune diseases and cancer. A diverse set of pharmacological strategies is emerging, ranging from targeted inhibitors of peptide-processing enzymes to epigenetic modulators that increase antigen visibility. These approaches aim to reshape the repertoire of peptides presented on MHC molecules. Collectively, these drugs illustrate the growing potential of manipulating antigen presentation as a therapeutic strategy. By selectively influencing peptide generation, processing, and presentation, these compounds can either enhance immune detection of malignant cells or temper aberrant immune activation in autoimmune diseases. Continued clinical investigation will clarify their optimal use and may establish antigen-presentation modulation as a cornerstone of next-generation immunotherapies.

Conclusion

The modulation of antigen presentation represents a rapidly evolving and highly promising therapeutic strategy for both cancer and autoimmune diseases. Advances in our understanding of the molecular machinery governing peptide processing, MHC loading, and antigen display have enabled the rational development of drugs that directly alter these pathways. In oncology, agents such as ER aminopeptidase inhibitors, immunoproteasome modulators, and epigenetic drugs can reshape the immunopeptidome, enhance MHC expression, or restore tumor visibility to cytotoxic T cells, thereby augmenting the efficacy of immunotherapies and potentially overcoming resistance mechanisms. Conversely, in autoimmune disease, selective inhibition of components such as the immunoproteasome or ERAP enzymes can reduce the presentation of self-antigens, dampening pathogenic T cell activation and alleviating tissue inflammation without broadly suppressing systemic immunity.

Despite these advances, significant challenges remain. The specificity of antigen presentation modulation must be carefully controlled to avoid off-target effects, including unintended immunogenicity in cancer or exacerbation of autoimmunity in non-target tissues. Moreover, the heterogeneous nature of both tumor antigen repertoires and autoimmune targets necessitates a personalized approach to therapy design, supported by biomarker-guided patient selection. Combination strategies, linking antigen presentation modulators with checkpoint inhibitors, vaccines, or conventional immunosuppressive agents, appear particularly promising, but require rigorous clinical evaluation to optimize efficacy while minimizing toxicity.

Overall, drugs that directly target antigen processing and presentation constitute a mechanistically distinct and versatile class of immunomodulators. Their continued development, guided by advances in molecular immunology and precision medicine, holds the potential to transform therapeutic paradigms in both cancer and autoimmune disease. Future research should focus on elucidating the full spectrum of immunopeptidomic changes induced by these agents, defining predictive biomarkers of response, and integrating these drugs into rational combination regimens that maximize clinical benefit while minimizing immune-related adverse events.

Table 2. Examples of mechanistically distinct drugs that suppress antigen-presentation for autoimmune disease

Class	Mechanism of action	Autoimmune disease	Development stage
Small-molecule selective immunoproteasome inhibitor	Selectively inhibits immunoproteasome catalytic subunits (e.g., LMP7/β5i) changes peptide generation and reduces antigen presentation plus inflammatory cytokine production.	Systemic lupus erythematosus / lupus nephritis (and other autoimmune indications).	Clinical: Phase 1b/2 studies completed; mid-stage lupus nephritis trial paused/under regulatory review after safety signals, active program with continuing studies in other indications.
Small-molecule Cathepsin S inhibitor	Inhibits cathepsin S in endolysosomes, blocks invariant chain processing and MHC-II peptide loading (Lip10 accumulation biomarker), reducing $CD4^+$ T-cell activation.	CD4-T cell driven diseases (e.g., primary Sjögren's syndrome; studied in RA models).	Early clinical / pharmacodynamic studies with Lip10 biomarker validated; development reported in early trials.
Small-molecule or peptide TAP (Transporter associated with antigen processing) inhibitors	Block peptide translocation into the ER by inhibiting TAP → reduce supply of peptides for MHC-I loading, altering MHC-I presentation.	Explored conceptually for autoimmune contexts where reducing MHC-I presentation may be beneficial (preclinical).	Largely preclinical / discovery stage; TAP inhibitors have been identified (including viral-derived peptide mimetics and small-molecule leads).
Biologicals / small molecules (conceptual modulators of HLA-DM / HLA-DO)	Modulate peptide exchange/editing on MHC-II (HLA-DM is the peptide editor), change the peptide repertoire presented by MHC-II to $CD4^+$ T cells.	Conceptually applicable to CD4-driven autoimmune diseases; currently a research direction.	Mostly mechanistic and preclinical work (protein-interaction and structural studies); experimental modulators in discovery.

Table 3. Examples of mechanistically distinct drugs that enhance antigen-presentation for cancer therapy

Class / Type	Mechanism of action	Disease indication	Development stage / status
Small-molecule inhibitor of ER aminopeptidase 1 (ERAP1)	Inhibits ERAP1, changes trimming of peptides in ER, which peptides are loaded onto MHC-I, potentially reveals neo antigens for T cell recognition.	Solid tumors (various)	Phase 1/2 clinical trial (monotherapy and combo with PD-1 inhibitor)
Small-molecule immunoproteasome activator	Activates immuno proteasome catalytic activity, increases degradation of intracellular proteins, boosting peptide generation, expands diversity and abundance of MHC-I–bound peptides, enhances antigen presentation.	Multiple myeloma proposed immunotherapy enhancer	Preclinical (in vitro and mouse xenograft)
Small-molecule SMAC mimetic (IAP inhibitor)	Indirectly upregulates MHC-I expression (via NF-κB / downstream signaling) without increasing PD-L1, making tumor cells more visible to $CD8^+$ T cells.	Cancer (tumors with low MHC-I expression) proposed as adjuvant to immunotherapy	Preclinical (cell-line studies) showing enhanced T cell–mediated killing & ICB synergy.
Epigenetic modulator / histone deacetylase inhibitor	Increases transcription of genes for antigen presentation machinery (MHC-I, TAP1/2, proteasome components, β2-microglobulin, etc.) raises MHC-I surface expression and enhances antigen presentation.	Various cancers, especially “cold” tumors with low antigen presentation	Clinical use in cancer, being studied in combination with immunotherapies / cancer vaccines.
Monoclonal antibody or inhibitor repurposed for immunomodulation	Blocks PCSK9, which normally binds MHC-I and targets it for lysosomal degradation, inhibition increases MHC-I recycling to cell surface, enhances antigen presentation on tumor cells.	Cancer, proposed immunotherapy adjuvant	Preclinical / early translational research; not yet standard immunotherapy use.