



Review Article

The Altered Self-Antigen Recognition (ASAR) Hypothesis: A Noval Reading of Autoimmunity and Immune-Mediated Diseases Initiation and Persistence

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Received: Aug 9, 2026/ Revised: Sept 16, 2026/Accepted: Sept 20, 2026

Abstract

Immune-mediated diseases are traditionally interpreted through the hypothesis of impaired immune tolerance, autoreactive lymphocyte activation, and dysregulated inflammatory responses. While these mechanisms explain important aspects of disease progression, they do not fully clarify why immune responses demonstrate remarkable tissue specificity, selective antigen targeting, and distinct temporal patterns across different diseases. The hypothesis will introduce the Altered Self-Antigen Recognition (ASAR) hypothesis, a conceptual hypothesis proposing that, in a subset of immune-mediated diseases, the earliest initiating events may involve molecular alterations occurring within susceptible tissues before the establishment of chronic immune pathology. The ASAR hypothesis proposes that cellular stress, metabolic imbalance, oxidative injury, defective protein processing, or other disturbances of tissue homeostasis may generate Altered Self-Antigens through mechanisms including posttranslational modifications, abnormal peptide processing, structural changes, and impaired molecular clearance. These altered molecular structures may subsequently become recognized by adaptive immune mechanisms through genetically determined antigen presentation pathways, particularly HLA-dependent peptide presentation. Within this hypothesis, immune activation is not viewed solely as an initial failure of self-tolerance, but as a highly specific biological response to a modified molecular state generated within stressed tissues. Chronic disease progression may then result from sustained antigen generation, epitope spreading, persistent antigen presentation, inflammatory amplification, and failure of tissue restoration. The ASAR hypothesis is examined across representative immune-mediated diseases, including Type 1 Diabetes Mellitus, Celiac Disease, Multiple Sclerosis, Rheumatoid Arthritis, Hashimoto's Thyroiditis, Crohn's Disease, Systemic Lupus Erythematosus, and Myasthenia Gravis. Across these conditions, recurring biological patterns suggest potential interactions between tissue stress, altered molecular identity, immune recognition, and chronic inflammation. In conclusion This document introduces the theory in which that the Altered Self-Antigen Recognition (ASAR) hypothesis, proposing that tissue-specific molecular alterations precede and initiate immune-mediated diseases.

Keywords: Altered self-antigens; Autoimmunity; Antigen recognition; Immune tolerance; Tissue-specific inflammation

Introduction

Immunological-mediated diseases include a wide range of conditions in which genetic vulnerability, environmental exposures, tissue biology, and immunological control interact to create chronic pathological inflammation. (Kumar et al., 2025). Although the anatomical targets and clinical

manifestations of these diseases vary greatly, many have common immunological aspects, such as autoreactive T- and B-cell responses, autoantibody synthesis, antigen-specific immune recognition, and persistent tissue harm. (Rojas et al., 2024; Abeles et al., 2024). An important biological question remains insufficiently resolved: what determines the molecular identity of the tissue that becomes the target of the

immune response in the first place? In which that briefly discussed as the following points .

Tissue-Centered Model of Autoimmunity

- The ASAR hypothesis suggests tissue molecular alterations may precede immune activation in some diseases.
- Cellular stress, metabolic imbalance, and defective clearance generate altered self-antigens recognized by the immune system.

Molecular Alterations in Tissues

Tissue stress causes modifications like post-translational changes, oxidative damage, or abnormal protein processing. These alterations create structures that differ from normal self, increasing immunogenic potential.

Immune Recognition and Antigen Presentation

- Altered self-antigens are processed and presented via HLA-dependent pathways.
- Genetic variations in HLA influence which modified peptides are recognized by T cells. (Klein & Petrozziello, 2025; Arshad et al., 2025)

Disease Initiation and Progression

- Persistent tissue stress continuously produces altered self-antigens, triggering immune responses.
- Chronic disease involves mechanisms like epitope spreading, inflammation, and defective clearance maintaining pathology. (Strizzi et al., 2024) (Li et al., 2024; Xing et al., 2024)

Role of Tissue Stress and Cellular Damage

- Cellular stress responses disrupt protein folding and increase biochemical modifications.
- Ongoing tissue injury sustains molecular alterations, fueling immune activation.

Tolerance and Autoimmunity

- Immune tolerance is maintained through complementary mechanisms operating at different stages of lymphocyte development and activation. (Klein & Petrozziello, 2025)
- A susceptible individual may possess the immunological capacity to recognize an altered self-antigen, while the nature of the tissue alteration determines which antigen becomes visible and which organ becomes preferentially affected.
- Immune tolerance mechanisms remain vital but may not prevent recognition of altered self.
- Disease may start with tissue changes, with immune dysregulation contributing to chronicity.
- Within the present study , raises a fundamental question concerning disease initiation : Does immune-mediated pathology always begin with a primary failure of immune recognition, or can

molecular alterations within susceptible tissues precede and contribute to the initiation of immune recognition?

Chronic Disease Maintenance

- Persistent tissue stress and immune responses create a self-amplifying cycle.
- Factors like epitope spreading and impaired clearance sustain long-term inflammation and damage. (Strizzi et al., 2024)
- Under this hypothesis, immune tolerance remains essential but may not represent the complete explanation for disease initiation. Instead, tissue molecular alteration and immune regulation may constitute sequential and interacting components of the disease process.
- The hypothesis emphasizes the contrast between disease genesis and maintenance. Even if an altered self-antigen causes immune recognition, chronic illness cannot be attributed only to antigen production. Once adaptive immunity is established, mechanisms such as epitope spreading, prolonged antigen presentation, inflammatory amplification, memory-cell generation, poor clearance, and secondary tissue injury can sustain the pathogenic response.

Molecular Changes in Tissue Under Stress

- Chronic tissue stress causes abnormal protein processing and generation of modified self-peptides, including insulin-related and other β -cell antigens. (Lytrivi et al., 2025; Eizirik et al., 2023; Wang et al., 2025).
- These molecular alterations can persist and continuously stimulate the immune system, even without immune dysregulation.

Epitope Spreading and Disease Progression

- Initial immune responses target specific altered self-antigens, but tissue injury exposes new epitopes, broadening the autoimmune attack.
- This process transforms a focused response into a complex, widespread autoimmune process through secondary molecular changes. (Strizzi et al., 2024).
- This model might be generates a specific and experimentally testable prediction: in at least some immune-mediated diseases, molecular alterations within susceptible tissues should be detectable before, or at the earliest stages of, established adaptive immune activation and irreversible tissue destruction.

Self-Amplifying Cycle of Inflammation

- Immune activation releases cytokines like TNF- α , IFN- γ , and IL-1 β , which induce oxidative stress and cellular dysfunction. (Neurath, 2024)
- These inflammatory mediators generate additional molecular alterations, creating a feedback loop that sustains and amplifies tissue damage.
- The distinction between self and non-self has traditionally occupied a central position in immunology. The immune system must eliminate infectious and potentially harmful agents while maintaining tolerance toward the organism's own tissues.
- This balance is established through multiple layers of immune regulation, including central tolerance, peripheral tolerance, regulatory lymphocyte activity, antigen sequestration, and controlled antigen presentation. (Klein & Petrozziello, 2025).

Persistent Antigen Presentation in Chronic Disease

- Continuous availability of altered cellular components maintains antigen presentation by dendritic cells and macrophages.
- Persistent presentation prevents immune resolution, sustaining auto reactive T and B cell activation and memory cell survival.
- Adaptive immune recognition involves converting intracellular and extracellular proteins into molecular forms that can be presented to lymphocytes.
- Genetic variation within HLA molecules can alter peptide-binding preferences and influence which molecular structures are efficiently presented to T cells. This provides an important mechanistic basis for the strong association between specific HLA alleles and susceptibility to autoimmune and immune-mediated diseases.
- The HLA genotype does not determine the peptides produced within a tissue. Immune recognition indicates a relationship between the features of the immune system and the molecular state of the tissue under observation.. (Klein & Petrozziello, 2025; Arshad et al., 2025).

Impaired Clearance and Tissue Homeostasis Loss

- Defective removal of damaged or apoptotic cells leads to prolonged exposure to modified nuclear and cellular antigens. (Li et al., 2024; Xing et al., 2024).
- This persistence promotes secondary molecular changes and ongoing immune stimulation, exemplified in systemic lupus erythematosus.

Application to Specific Diseases

- The hypothesis links tissue stress and molecular alterations to immune recognition in diseases like Type 1 Diabetes, Celiac Disease, MS, RA, Hashimoto's, Crohn's, SLE, and Myasthenia Gravis.
- For example, β -cell stress in diabetes produces altered insulin peptides; gluten modification in celiac enhances immune recognition; myelin and neuronal protein changes in MS and MG initiate immune responses. (Sollid, 2024) (Lytrivi et al., 2025; Eizirik et al., 2023; Wang et al., 2025)
- Other examples from immune-mediated disorders demonstrate this basic premise. Citrullination in rheumatoid arthritis, enzymatic modification of gluten-derived peptides in celiac disease, stressed pancreatic β -cells can generate unconventional antigenic peptides in type 1 diabetes, and cellular injury and defective clearance can alter the availability and presentation of intracellular components in systemic autoimmune disease.. (Klein & Petrozziello, 2025; Arshad et al., 2025) (Raposo et al., 2024; Arshad et al., 2025).

Key Mechanisms Across Diseases

- Tissue-specific stress leads to generation of altered self-antigens.
- These structures are presented via HLA molecules, triggering immune recognition.
- Chronic inflammation and epitope spreading perpetuate tissue damage and immune activation. (Strizzi et al., 2024).

Comparison with Classical Autoimmunity

- Unlike traditional models focusing on immune tolerance failure, the hypothesis emphasizes tissue molecular alterations as initial triggers.
- Tissue-specific features and molecular modifications explain why systemic susceptibility genes result in tissue-specific diseases.

Autoantibodies as Molecular Sensors

- Autoantibodies may recognize modified self-antigens rather than unaltered structures.
- Their presence indicates molecular changes, not necessarily immune tolerance failure.

Testing and Validation Strategies

- Longitudinal studies aim to detect altered self-antigens before immune activation.
- Technologies like HLA immunopeptidomics and spatial proteomics identify early tissue changes. (Arshad et al., 2025).

- Animal models test if induced molecular alterations can trigger immune responses.

Future Directions and Implications

- Preventing molecular alterations could reduce immune activation.
- Biomarkers based on tissue stress and altered antigens may enable early diagnosis.
- The hypothesis encourages investigating tissue biology alongside immune regulation to understand disease initiation.

Mechanisms of Altered Self-Antigen Generation:

- Tissue stress (such as metabolic, oxidative, or endoplasmic reticulum stress), defective protein processing, or impaired molecular clearance can modify endogenous proteins. These modifications include posttranslational changes (e.g., citrullination, deamidation), abnormal folding, or structural alterations. (Raposo et al., 2024; Arshad et al., 2025) (Li et al., 2024; Xing et al., 2024)
- The altered molecules are then processed and presented by antigen-presenting cells (via HLA molecules), making them visible to the adaptive immune system. (Klein & Petrozziello, 2025; Arshad et al., 2025)

3. Sequential Model of Disease Initiation (ASAR Cascade):

1. Tissue susceptibility and stress (genetic/environmental factors)
2. Molecular alteration within the tissue
3. Generation of altered self-antigens
4. Antigen processing and HLA-dependent presentation
5. Adaptive immune recognition
6. Immune amplification and chronic tissue injury

4. Distinction from Classical Autoimmunity:

- The classical model focuses on immune system failures (loss of tolerance, auto reactive lymphocytes) as the primary cause.
- ASAR shifts the focus to the tissue: it asks what changes in the tissue make it immunologically visible as "altered," thus triggering immune recognition.
- Both models are not mutually exclusive; ASAR adds an earlier, tissue-centered layer to the disease timeline.

5. Examples Across Diseases:

- Rheumatoid Arthritis: Citrullination of proteins in joints creates new antigenic targets before immune attack. (Raposo et al., 2024; Arshad et al., 2025)
- Celiac Disease: Gluten peptides are enzymatically modified in the gut, increasing their immunogenicity. (Sollid, 2024)
- Type 1 Diabetes: Stressed pancreatic beta cells generate altered insulin-related peptides, which become immune targets.
- Systemic Lupus Erythematosus: Defective clearance of apoptotic cells leads to accumulation of altered nuclear antigens. (Li et al., 2024; Xing et al., 2024)

7. Implications and Predictions:

- ASAR predicts that altered self-antigens should be detectable before or at the earliest stages of immune activation.
- It suggests new avenues for early biomarkers, preventive strategies, and therapies aimed at restoring tissue molecular integrity before irreversible immune-mediated damage occurs.
- Experimental validation will require advanced molecular profiling, immunopeptidomics, and longitudinal studies. (Arshad et al., 2025).

How the ASAR Hypothesis Could Reshape Diagnostic Criteria for Autoimmune Diseases

It appears there might be a specific acronym mix-up or a very specialized or emerging concept in your query, as a universal "ASAR Hypothesis" is not widely recognized in mainstream rheumatology or immunology for reshaping autoimmune diagnostic criteria.

American College of Rheumatology and European Alliance of Associations for Rheumatology) are moving toward data-driven, highly specific architectures rather than broad clinical checklists. If an emerging model like ASAR focuses on phenotypic registry data, machine learning, or risk-stratification, it typically impacts diagnosis in specific ways, the following point might be illustrated briefly.

1. Shift from Immune-Centered to Tissue-Centered Diagnostics

The shift from immune-centered to tissue-centered diagnostics marks a medical transition from measuring generalized systemic inflammation in the blood to analyzing localized, microenvironmental cell states, spatial organization, and structural changes directly within affected organs

- **Classical Model:** Focuses on detecting immune system abnormalities (auto-antibodies, autoreactive lymphocytes, inflammatory markers) and evidence of tissue damage. Focuses on circulating white

blood cells, systemic antibodies, and broad cytokine profiles in blood or serum.

- **ASAR Model:** Proposes that molecular alterations within tissues (such as posttranslational modifications, abnormal protein processing, or defective clearance) may precede immune activation. Diagnostics would shift to detecting these early tissue changes—before overt immune or clinical manifestations. Analyzes local cellular niches, organ-specific residency, extracellular matrix interactions, and micro-anatomical changes

2. Earlier Detection Through Molecular Biomarkers

- **ASAR Prediction:** Altered selfantigens and tissue stress signatures should be detectable before or at the earliest stages of immune activation.
- **Diagnostic Implication:** New biomarkers could include:
 - Modified peptides (e.g., citrullinated proteins in rheumatoid arthritis, deamidated gluten peptides in celiac disease)
 - Abnormal protein conformations or stress-induced molecular signatures (e.g., markers of endoplasmic reticulum or oxidative stress)
 - Altered HLA peptide repertoires identified by immunopeptidomics
- **Example:** In rheumatoid arthritis, anticitrullinated protein antibodies (ACPAs) can appear years before clinical symptoms. ASAR suggests expanding this approach to other diseases by searching for disease-specific altered self-antigens as early diagnostic markers.

3. Disease Risk Stratification and Preclinical Diagnosis

The target goal for present theory to identifies pre-clinical regional dysfunction before whole-body symptoms appear.

ASAR Contribution: By identifying individuals with early tissue molecular alterations (even before immune activation), clinicians could stratify risk and monitor high-risk populations more effectively.

- **Example:** In type 1 diabetes, longitudinal monitoring for altered beta-cell peptides or stress markers could identify atrisk individuals before autoantibody seroconversion or hyperglycemia.

4. Redefining Disease Onset and Progression

- **Current Criteria:** Disease onset is typically defined by the appearance of immune markers or clinical symptoms.
- **ASAR**

Informed Criteria: Disease onset could be redefined as the point when tissue molecular alterations become detectable, even in the absence of immune or clinical signs. This would allow for a new category of "preclinical" or "molecular-stage" autoimmune disease.

5. Integration of Advanced Molecular Technologies

- **ASAR Driven Diagnostics:**

Single-Cell RNA Sequencing: Maps distinct cell populations across specific

-Spatial Multi-Omics: Preserves the 3D and in situ architectural context of cellular signaling. non-lymphoid tissues.

- Digital Immune Modeling: Evaluates individual organ microenvironments rather than generalized system status.

- **Example:** In celiac disease, detection of deamidated gluten peptides and tissue transglutaminase activity in at-risk individuals could precede serological or histological changes.

6. Preventive and Personalized Medicine Opportunities

- **ASAR Implication:** Early identification of tissue molecular alterations could enable preventive interventions (e.g., reducing tissue stress, blocking specific modifying enzymes) before irreversible immune mediated damage occurs.
- **Example:** In rheumatoid arthritis, therapies targeting citrullination pathways could be considered in individuals with molecular evidence of altered self-antigen formation but no clinical arthritis.

8. Experimental Validation and Future Directions

- **ASAR's Testable Predictions:**
 - Altered self-antigens should be detectable before immune activation.
 - Preventing or reversing tissue molecular alterations should reduce disease risk.
- **Diagnostic Evolution:** If validated, diagnostic criteria would expand to include molecular and tissue-based markers, not just immune or clinical endpoints.

Summary Table: Classical vs. ASAR-Informed Diagnostic Criteria :

Aspect	Classical Autoimmunity Model	ASAR Hypothesis Model
Primary Focus	Immune system markers, tissue damage	Tissue molecular alterations
Earliest Detection	Autoantibodies, immune activation	Altered self-antigens, stress markers
Disease Onset	Immune/clinical signs	Molecular/tissue changes
Biomarker Examples	ANA, RF, ACPAs	Citrullinated proteins, deamidated peptides, stress signatures
Diagnostic Tools	Serology, histology, imaging	Immunopeptidomics , proteomics, single-cell omics

Comparison: Classical Autoimmunity Paradigm vs. ASAR Hypothesis

Aspect	Classical Autoimmunity Paradigm	Altered Self-Antigen Recognition (ASAR) Hypothesis
Primary Focus	Immune system dysfunction (failure of central/peripheral tolerance, autoreactive lymphocyte activation)	Tissue-centered: molecular alterations within stressed tissues generate altered self-antigens
Disease Initiation	Begins with immune tolerance failure; autoreactive cells attack normal self-antigens	Begins with tissue stress or injury causing molecular changes; altered self-antigens are generated and then recognized by the immune system
Sequence of Events	Genetic susceptibility → Immune tolerance failure → Autoreactive lymphocyte activation → Immune attack on self → Tissue damage	Genetic susceptibility + tissue/environmental stress → Molecular alteration in tissue → Altered self-antigen generation → HLA-dependent antigen presentation → Adaptive immune recognition → Chronic immune-mediated damage
Tissue Specificity	Not fully explained; same immune risk genes can lead to different tissue targets	Determined by which tissue first undergoes molecular alteration; tissue biology and stress responses shape disease location
Role of Autoantibodies	Evidence of immune system attacking self; marker of tolerance failure	May reflect immune recognition of altered (not normal) self-antigens; autoantibodies can act as sensors of molecular change
Chronic Disease Maintenance	Driven by persistent immune dysregulation, memory cells, epitope spreading	Driven by ongoing tissue stress, continuous altered antigen generation, immune amplification, and feedback loops
Implications for Diagnosis	Focus on detecting immune markers (autoantibodies, autoreactive cells) and tissue damage	Suggests early detection of tissue molecular alterations (e.g., modified peptides, stress markers) before immune activation
Therapeutic Implications	Target immune system (immunosuppression, tolerance induction)	Potential to target tissue stress, prevent molecular alteration, or restore tissue integrity before immune activation

Disease-Specific Applications of the Altered Self-Antigen Recognition (ASAR) Hypothesis

Type 1 Diabetes Mellitus: Living β -Cell Alteration and Emergence of Neoantigenic Peptides :

Type 1 diabetes is caused by an immunological response to pancreatic β -cell antigens such as insulin/proinsulin, GAD65, IA-2, and ZnT8. Autoantibodies to these antigens can emerge before clinical diabetes, making them significant indicators of

disease progression. Importantly, β -cell antigens may not always be conventional native proteins. **Hybrid insulin peptides (HIPs)**, produced through altered peptide processing, can act as neoantigens and be recognized by T cells. (Jia & Yu, 2024).

From the **ASAR framework**, chronic β -cell stress may cause changes in protein processing, peptide generation, intracellular trafficking, and antigen availability. These changes could create **new or altered peptide repertoires (neoepitopes)** that

are subsequently presented by HLA molecules and recognized by T and B cells.

Proposed ASAR sequence:

β -cell stress $\rightarrow$ altered protein processing $\rightarrow$ altered peptide repertoire/neoepitopes $\rightarrow$ HLA presentation $\rightarrow$ T/B-cell recognition $\rightarrow$ islet autoantibodies $\rightarrow$ T1D progression. The key ASAR prediction is that **molecular alterations in β -cell antigens or the β -cell immunopeptidome may be detectable before, or at the earliest stages of, autoantibody seroconversion**, potentially providing an earlier window for understanding or detecting T1D development.

Hashimoto's Thyroiditis: Altered Thyrocyte Antigenic Landscape

Hashimoto's thyroiditis is characterized by autoimmune reactions to thyroid antigens, primarily TPO and thyroglobulin (Tg), with anti-TPO and anti-Tg antibodies serving as significant markers of thyroid autoimmunity. However, ASAR posits that molecular alterations in thyroid cells may occur prior to or during autoimmunity, as a result of oxidative, inflammatory, or metabolic stress. These alterations may affect protein processing and peptide presentation, potentially resulting in changed or neoantigenic peptides that activate immune recognition.. (Li et al., 2024).

Coeliac disease :

Celiac disease serves as a suitable mechanistic model for ASAR, despite the fact that the initial antigen (gluten/gliadin) is not self-derived. In patients with HLA-DQ2 or HLA-DQ8, the enzyme tissue transglutaminase 2 (TG2) deamidates gliadin peptides, boosting their binding to HLA molecules and T-cell recognition. Thus, TG2 can change the molecular structure of an antigen and improve its immunological visibility.. (Arentz-Hansen et al., 2000; Kim et al., 2004).

The ASAR-relevant sequence is :

Celiac disease illustrates the ASAR principle that **molecular modification can increase an antigen's visibility to the immune system**. TG2 modifies gluten-derived peptides, enhancing HLA binding and T-cell activation, leading to B-cell responses and intestinal injury. However, unlike classical ASAR, **the initiating antigen is external (gluten), not an altered self-antigen**.

Rheumatoid arthritis :

Rheumatoid arthritis (RA) strongly supports the ASAR idea since self-proteins can become immunogenic through molecular alteration. PAD enzymes convert arginine to citrulline (citrullination), resulting in altered protein epitopes that can produce ACPA. Significantly, these autoantibodies

may arise years before clinical arthritis, indicating that changed self-antigens can precede disease presentation.. (Ma et al., 2024).

In RA, **post-translational modifications** such as citrullination and carbamylation can alter normal self-proteins, creating modified epitopes that become targets of the immune system and lead to **ACPA or anti-carbamylated protein antibodies**. This supports the ASAR concept that **altered self-proteins may precede and facilitate autoimmunity**, although the exact timing between protein modification and the initial immune response remains uncertain. (Raposo et al., 2024).

Systemic lupus (SLE) :

SLE is defined by autoimmunity to intracellular and nuclear antigens such as DNA, nucleosomes, Sm, Ro/SSA, and La/SSB. Defective efferocytosis permits apoptotic cellular material to remain and undergo alteration, making it more accessible to antigen-presenting cells.. (Li et al., 2024).

ASAR pathway in SLE:

Cell death $\rightarrow$ defective clearance $\rightarrow$ persistence $\rightarrow$ modification/exposure $\rightarrow$ antigen presentation $\rightarrow$ autoreactive B/T-cell activation $\rightarrow$ autoantibodies

Thus, ASAR suggests that self-antigens do not necessarily need to be inherently abnormal; their **altered persistence, processing, chemical modification, or exposure after cell death** may make them immunogenic. This represents the **dying-cell/clearance pathway** of ASAR.

ANCA associated diseases :

ANCA-associated vasculitis is caused by autoantibodies against PR3 and MPO, which are normally found inside neutrophils. Neutrophil activation and NET creation can move and expose these antigens, making them available for the immune system.. (Bettacchioli et al., 2024).

ASAR pathway:

Neutrophil stress/activation $\rightarrow$ altered antigen localization $\rightarrow$ PR3/MPO exposure $\rightarrow$ immune recognition $\rightarrow$ ANCA activation $\rightarrow$ NETosis $\rightarrow$ further antigen exposure

This suggests a **positive feedback loop** in which cellular stress and immune activation reinforce each other. ASAR specifically proposes that changes in antigen localization or molecular state may **precede the initial autoantibody response**.

Myasthenia gravis (MG)

Myasthenia gravis (MG) is characterized by autoantibodies against AChR, MuSK, or LRP4, which disrupt neuromuscular transmission via various mechanisms. From the ASAR perspective, local stress or remodeling at the neuromuscular

junction may change antigen accessibility, conformation, or trafficking, enhancing immune recognition.. (Mousavi et al., 2024; Chuquisana et al., 2024).

ASAR pathway:

NMJ stress/remodeling → altered antigen state/accessibility → immune recognition → autoantibodies → impaired neuromuscular transmission
The antibody targets and their pathogenic effects are established, while the proposed **initial tissue alteration remains a testable ASAR hypothesis**.

Anti-NMDA receptor encephalitis involves antibodies against the **GluN1/NR1 subunit** of the NMDA receptor. The established evidence shows that antibody recognition depends on the receptor's **3D structure and accessibility**.

ASAR proposes that **neuronal stress, altered receptor trafficking, post-translational modification, or conformational changes** may increase GluN1 accessibility before antibody development.

ASAR pathway:

Neuronal stress → altered GluN1 conformation/accessibility → immune recognition → anti-GluN1 antibodies → receptor internalization → neuronal dysfunction

The antibody–GluN1 interaction is established, while the **preceding molecular alteration remains a testable hypothesis**.

Primary biliary cholangitis (PBC) :-

Primary biliary cholangitis (PBC) is characterized by autoimmune damage of tiny bile ducts and immunological responses to PDC-E2, including antimitochochondrial antibodies (AMA). Because PDC-E2 is found in numerous organs, its identification does not explain why the bile ducts are selectively targeted. ASAR proposes that **biliary and mitochondrial stress** may alter PDC-E2 accessibility, processing, or molecular state, increasing its immune visibility in biliary epithelial cells.

ASAR pathway:

Biliary/mitochondrial stress → altered PDC-E2 state/accessibility → antigen presentation → immune recognition → AMA/T-cell response → biliary injury → further antigen exposure

Thus, ASAR emphasizes the **tissue-specific molecular context** rather than requiring PDC-E2 itself to be a newly created antigen.

Pemphigus vulgaris (PV)

Pemphigus vulgaris (PV) is an autoimmune blistering illness characterized by antibodies to desmoglein 3 (Dsg3) and desmoglein 1. Antibody recognition can target several areas of these proteins, and antibody specificity may alter over time, indicating antigenic evolution.. (Tavakolpour et al., 2024).

ASAR proposes that **epithelial stress or alterations in desmosomal proteins** could modify their conformation, processing, or accessibility, increasing immune recognition.

ASAR pathway:

Epithelial stress → altered Dsg state/accessibility → immune recognition → anti-Dsg3/Dsg1 antibodies → loss of adhesion → tissue injury → further antigen exposure
The changing antibody repertoire supports a possible **feedback between tissue injury and antigenic evolution**, while the claim that Dsg alteration precedes the initial autoimmune response remains unproven.

Integrative Interpretation of the Ten Diseases

The ten diseases are not identical but can be grouped into **three ASAR-related biological pathways**. The **Living-Cell Alteration pathway** involves situations where the antigen-producing cell remains alive but undergoes **stress, remodeling, or molecular changes** that alter its antigenic profile.

Representative diseases: T1D, Hashimoto's thyroiditis, myasthenia gravis, anti-NMDAR encephalitis, pemphigus vulgaris, and PBC.

ASAR sequence:

Living-cell stress/remodeling → altered self-proteins/peptides → increased antigen accessibility/presentation → immune recognition → autoantibody formation.

B. Post-Translationally Modified Self:
This pathway is strongly represented by **rheumatoid arthritis (RA)**, where modifications such as **citrullination and carbamylation** change normal self-proteins, creating altered epitopes that can trigger immune recognition.

Sequence:

Native self-protein → PTM → altered molecular identity → modified epitope → immune recognition

C. Dying-Cell / Altered-Exposure Pathway:
Seen mainly in **SLE and ANCA-associated vasculitis**, where cell death, defective clearance, or cellular activation increases exposure of normally hidden antigens, promoting immune recognition and tissue injury.

Sequence:

Cell stress/death → altered clearance/exposure → persistence/modification → antigen presentation → immune recognition → tissue injury.

Tissue specificity :

ASAR proposes that autoimmune diseases may target specific tissues because each tissue has a unique **biological and molecular environment**. In which have different factors include:

- **Metabolism:** Different tissues have different metabolic demands and stress levels.
- **Cellular stress:** Tissue-specific responses to oxidative, inflammatory, or metabolic stress may alter self-proteins.
- **Protein expression:** Some self-proteins are predominantly or uniquely expressed in particular tissues.
- **Local environment:** Microbes, toxins, inflammation, or other exposures may affect antigen formation.
- **Molecular processing:** Tissues may process, modify, or present proteins differently.
- **Antigen generation:** Local conditions may promote production of altered or novel antigenic peptides.

ASAR concept:

Tissue-specific stress/alteration → altered antigen → increased immune visibility → localized immune recognition → tissue-specific autoimmune injury. Thus, the **tissue itself may help determine where autoimmune disease begins and why particular organs become preferential targets.**

Conclusions

The **ASAR hypothesis** proposes that autoimmunity may begin when **self-tissues undergo molecular changes** before immune recognition occurs. Stress, oxidative damage, abnormal protein processing, post-translational modifications, altered antigen localization, or defective clearance may create **altered self-antigens** that become more visible to the immune system.

ASAR sequence

Tissue alteration → altered self-antigen → immune recognition → tissue injury → further antigen alteration → chronic autoimmunity

The key ASAR prediction is that **disease-relevant altered antigens should be detectable before antigen-specific immune responses**. If confirmed, this would suggest that autoimmunity may sometimes be a response not to the original self, but to a **biologically altered form of self**.

Author Contributions

The author has significantly contributed to the study's conception, design, data collection, analysis, and interpretation. All authors were involved in writing the manuscript or critically reviewing it for its intellectual value. They have reviewed and approved the final version for submission and publication and accept full responsibility for the content and integrity of the work.

Financial Support

The authors declare that no external funding was received for this study.

Conflicts of Interest

The authors state that there are no financial, personal, or professional conflicts of interest associated with this research.

Ethical Approvals

This research did not involve the use of human participants or animal subjects and therefore did not require ethical clearance

Publisher's Note

The Journal stays neutral about jurisdictional claims in published maps and institutional affiliations

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How to cite this article

Al Masoudi, A. S. T., & Al Mammori, R. T. O. (2026). The altered self-antigen recognition (ASAR) hypothesis: A novel reading of autoimmunity and immune-mediated diseases initiation and persistence. *Science Archives*, 7(3), 337–346. <https://doi.org/10.47587/SA.2026.7305>

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