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The Peptide Revolution in Autoimmune Disease: Mechanisms, Clinical Evidence, and Translational Potential

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ABSTRACT

Autoimmune diseases are a class of disorders where the immune system mistakenly attacks one's own body, causing chronic inflammation, prolonged morbidity, and progressive tissue damage. Immunosuppressive and biologic therapy, although used for disease control, was associated with incomplete efficacy, toxicity, and the risk of infections. The present review has focused on therapeutic peptides as immune modulators in autoimmune diseases and has described their mechanistic actions and the human evidence available.

The scope of the review included peptide-mediated modulation of antigen presentation, T cell differentiation, cytokine signaling, innate immune responses, and tissue repair. Human clinical and translational data were evaluated across multiple autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, psoriasis, and type 1 diabetes. Across these conditions, peptides showed continuous immunologic activity and, in general, good safety profiles in preclinical studies and early-phase clinical trials.

The review, however, concluded that the clinical benefits were still inconsistent and often modest. The majority of the studies were constrained by a limited number of participants, short follow-ups, diverse designs, and mainly relied on immunological or biomarker endpoints rather than sustainability in clinical outcomes as a measure of success. Long-term efficacy, best dosing, and comparative effectiveness were not adequately defined.

Keywords: Therapeutic peptides, immunomodulation, autoimmunity, multiple sclerosis, rheumatoid arthritis, lupus

INTRODUCTION

Conditions in which immune tolerance to self-antigens is lost, resulting in persistent inflammation, tissue damage, and organ failure, are known as autoimmune disorders. These conditions encompass a large volume of disorders, including organ-specific diseases such as type 1 diabetes mellitus (T1DM), as well as systemic conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [1-3]. Autoimmune diseases together constitute a significant global health burden and have shown a rising trend across diverse populations [2,3]. Heterogeneous clinical presentations, delayed diagnosis, and high

rates of comorbidities further complicate management and contribute to poorer outcomes [2,3].

Even though corticosteroids, disease-modifying antirheumatic drugs (DMARDs), biologics, and small-molecule inhibitors have improved disease control for many patients, therapeutic constraints persist. However, due to incomplete immune responses, immunosuppression-related risks, and significant cost implications, these options are limited [4,5]. Antigen-specific control, which reduces systemic suppression while reestablishing long-lasting immunological tolerance, is the focus of new strategies. This illustrates the need for a change to safer and more accurate therapeutic design [6].

In this context, peptides have reappeared as a potentially useful therapeutic class. Due to significant developments in peptide engineering, cyclization, PEGylation, nanoparticle-based distribution, and computational sequence optimization, peptide therapeutics, which were formerly constrained by stability and delivery problems, have seen a renaissance [7-10]. By improving peptide half-life, receptor selectivity, and tissue targeting, these advancements have made it possible to precisely engage immune mechanisms related to autoimmunity. Because they can mimic endogenous signaling molecules, affect antigen processing, regulate inflammatory cascades, and promote tissue healing in ways that support immune regulation, peptides occupy a physiologically intuitive niche [8,10].

Multiple mechanistic features position peptides as attractive candidates for autoimmune indications. Their structural flexibility enables the targeted modulation of T-cell differentiation, enhancement of regulatory T-cell activity, and an influence on dendritic cell and macrophage phenotypes [7-10]. Certain natural and synthetic peptides also promote tissue and barrier repair, a critical component of disease modification in gastrointestinal, cutaneous, and neurologic autoimmune disorders. Early translational and clinical studies, particularly those involving thymic peptides, antimicrobial-derived peptides, and engineered immunoregulatory analogues, demonstrate the modulation of immune biomarkers. However, sample sizes remain limited, and study designs are heterogeneous [7,8].

A clear reality check is warranted: randomized controlled trials assessing clinically meaningful endpoints remain limited for most peptide candidates. Many published reports rely on surrogate markers, short follow-up, or exploratory cohorts [4,5]. Long-term safety, optimal dosing, delivery routes, and comparative effectiveness remain underexplored. These gaps highlight the need for a structured synthesis of current human data and a translational roadmap to rigorously and ethically evaluate peptide therapy in autoimmune diseases.

This review integrates mechanistic understanding, human clinical data, and emerging therapeutic insights on peptide-based immunomodulation in autoimmunity. It aims to delineate where peptides hold genuine therapeutic promise, where evidence remains preliminary, and what research priorities are needed to advance the field.

OVERVIEW OF PEPTIDES IN IMMUNOMODULATION

Peptides are molecules formed by the condensation of amino acids via peptide bonds, typically comprising short chains of between ~2 and 50 residues, positioned between small molecules and full proteins in size and complexity. [11,12] In a therapeutic context, peptides are attractive because they retain sufficient structural specificity to engage defined molecular targets (such as receptors, antigen-presenting cell complexes, or immune synapse components) while avoiding many of the manufacturing, stability, and immunogenicity challenges associated with larger biologics. [11,12]

Peptides with immunomodulatory relevance can be categorized into several overlapping groups:

1. **Natural (endogenous) peptides -** These are peptides originally produced by the body (e.g., thymic peptides, antimicrobial peptides, neuropeptides) and serve physiological regulatory roles. For example, thymic peptides modulate T-cell development and immune tolerance, and antimicrobial peptides (AMPs) such as LL-37 act in both host-defence and immune regulation. [12,13]
2. **Synthetic peptides/peptidomimetics -** Designed in the laboratory to mimic, enhance, or alter natural peptide sequences. These may incorporate non-natural amino acids, backbone modifications, or cyclization to improve potency, stability, or target specificity. [14]
3. **Bioregulatory peptides -** Derived from tissue-specific peptide fractions (for example, fragments from thymus, brain, or vascular tissue) that regulate homeostasis and immune balance rather than act purely as antagonists or agonists of receptors. These often aim to restore immune equilibrium rather than fully suppress it. [13]
4. **Peptide analogues -** Variants of natural peptides engineered for improved pharmacokinetics or therapeutic profile (longer half-life, improved tissue penetration, modified receptor binding). Examples include analogues of AMPs, thymic peptides, or tolerogenic epitope peptides. [11,13]

These classifications help frame how different peptide therapies might be selected based on desired immune-modulatory outcome (restoration, suppression, repair) and pharmacologic constraints (delivery, stability).

Immunomodulatory peptides through the different adaptive, innate, and tissue-repair mechanisms control autoimmune inflammation without causing widespread suppression of the immune response. They affect the presentation of antigens, encourage T-cell regulatory responses, reduce the activation of autoreactive T-cells, and influence cytokine signaling, including the reduction of IL-6, TNF-α, and IFN-γ. [13-15] Along with that, quite a few peptide classes also facilitate epithelium and endothelium repair, which results in the strengthening of barrier integrity and tissue regrowth in locations affected by autoimmune disorders. [11,12,16]

THERAPEUTIC PEPTIDES IN AUTOIMMUNITY

Therapeutic peptides belong to the class of compounds that have the potential to modulate the immune system and are capable of affecting immune reactions in a highly precise and context-dependent manner, including the induction of antigen-specific T-cell responses, modulation of cytokine signaling, and regulation of overall immune activity. These immunomodulatory roles are sometimes even indirectly linked to functions like epithelial barrier and tissue repair in certain environmental conditions. [17,18] When it comes to the treatment of autoimmune diseases, the peptide-based strategies have been explored not as traditional immunosuppressants but as methods aimed at restoring immune tolerance or recalibrating the overactive immune pathways in the right way, as supported by animal models and early-phase clinical studies. [19]

Not only one or two but numerous classes of different types of peptide-based strategies recurring in autoimmune diseases are discussed, such as antigen-tolerogenic peptides, thymic peptides with immunomodulatory properties, naturally-occurring antimicrobial peptides having different immune activities depending on the context of their application, and, lastly, peptides that assist in maintaining barrier function/integrity or tissue repair [20]. On the other hand, the clinical usefulness of these approaches is highly disease-specific and is largely determined by the diversity of

the immune system, the tissue environment, and the route of administration; thus, it is crucial to apply a disease-centered framework in assessing peptide-based treatments for autoimmune conditions. [21]

Disease-Centred Overview of Therapeutic Peptides

Multiple Sclerosis (MS)

Multiple sclerosis is a demyelinating disease of the central nervous system (CNS) triggered by antigens and marked by the presence of autoreactive T cells, B-cell involvement, and chronic inflammation in the nervous system. [21,22] In the past, peptide-based methods in MS have been mainly focused on the myelin-derived peptides and their altered forms that were intended to create an antigen-specific tolerance by encouraging the response of the regulatory T cells, deviation of the immune system away from the pathogenic Th1/Th17 pathways, and the reduction of the activation of the autoreactive T cells. [21] Fewer but still significant immunologic or biomarker effects have been shown in multiple phase I/II clinical trials, which concluded that the peptide treatments were safe; however, the clinical efficacy was not consistent, and thus no peptide appeared as a definitive disease-modifying agent, hence also no peptide treatment came to be that was called the gold standard by all. [21] Thymic peptides such as thymosin-α1 have also exhibited immunomodulatory properties in small pilot studies but lack strong phase III evidence. [21,22] Among the translational challenges, the most important ones are the HLA heterogeneity, the spreading of the epitopes, and dynamic antigen targets over the disease course, which altogether limit durable clinical benefit. [21]

Rheumatoid Arthritis (RA)

Rheumatoid arthritis is an autoimmune disease that progresses slowly and is accompanied by synovial inflammation, caused by infiltration of autoreactive T cells, production of autoantibodies, and a network of proinflammatory cytokines, where TNF-α and IL-6 are the main factors, leading to the destruction of joints. [23-25] Peptide-based RA treatments have thus centered on causing antigen-specific immune tolerance or recalibrating the immune responses rather than suppressing the inflammatory cytokines directly. [24]

Citrullinated peptide vaccines and HSP60-derived altered peptide ligands like CIGB-814 have been the subject of early-phase human trials. [24] These strategies aim to create T-cell responses that are regulatory, to downregulate the activation of autoreactive T-cells, and to reduce the inflammatory signaling that occurs further down the line. [24] The results from the clinical studies so far are not only showing very few side effects but also a decrease in inflammation-related biomarkers, although only small-scale and slight improvements in patients' conditions have been noticed. However, there is still no robust phase III data on efficacy, which points out the stubborn translational gap between immunologic modulation and clinical disease control in RA that lasts over time. [24]

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is a heterogeneous, multisystem autoimmune disease characterized by loss of immune tolerance, autoantibody production, immune complex deposition, and dysregulated innate and adaptive immune responses, resulting in tissue inflammation and organ damage. [23,25] Defects in regulatory immune pathways, particularly impaired regulatory T-cell (Treg) function and aberrant cytokine signaling, play a central role in disease pathogenesis, providing a mechanistic rationale for peptide-based immunomodulatory strategies aimed at restoring immune balance rather than broadly suppressing immunity. [23]

SLE peptide-based strategies have mainly dealt with tolerogenic peptides and thymic immunomodulators that are aimed at strengthening immune regulation,

facilitating Treg activity, and extinguishing autoreactive lymphocyte responses. The early-phase and pilot clinical trials have reported usual safety profiles and minor immunologic effects, such as the changes in markers of immune activation, but these findings have not been consistently or reproducibly translated into clinical benefit in larger or more heterogeneous patient groups. [20] The intricacy and diversity of SLE, with different organs being involved at different times and the disease activity fluctuating, are still the main impediments to the clinical use of peptide-based therapies. [20]

Inflammatory Bowel Disease (IBD)

The chronic inflammatory disorders Crohn's disease and ulcerative colitis are characterized by the breakdown of the intestinal epithelial barrier, dysregulated mucosal immunity, and complex interactions between the gut microbiota and the host immune system, which, in concert, prolong inflammation and damage in the gut. [26] The underlying pathophysiology makes barrier-reinforcing and immune-modulating therapeutic strategies strong candidates, along with conventional anti-inflammatory treatments.

Currently, host-defense and barrier-modulating peptides are mostly examined in preclinical and translational research studies. Among such peptides is LL-37, the antimicrobial peptide (human cathelicidin), which is upregulated in inflammation and has the potential to alter the function of both epithelial and immune cells; however, so far, the supporting evidence is largely mechanistic and not based on demonstration of therapeutic benefit in well-controlled clinical settings. [26] The treatment with peptide fragments, like the α-melanocyte-stimulating hormone derivative KPV, has been suggested by animal studies to carry anti-inflammatory as well as epithelial-protective effects; however, those findings are still mainly preclinical. [26] BPC-157, the cytoprotective peptide, has been indicated through animal testing and small human exploratory case reports to be a contributor to gastrointestinal mucosal healing, but there is no such evidence through rigorously controlled clinical trials in autoimmune IBD populations so far. [26]

Psoriasis and Autoimmune Skin Disorders

Psoriasis is a chronic immune-mediated skin disease driven by innate immune activation, IL-23/IL-17 axis signaling, and the faulty communication between keratinocytes, dendritic cells, and T cells. In this context, the antimicrobial peptides contribute to the disease process rather than merely providing protection, which is the case with the cathelicidin peptide LL-37 that is significantly overproduced in psoriatic plaques. [27,28] Not only does it bind self-DNA and RNA, but it also enhances the activation of plasmacytoid dendritic cells and consequently the prolongation of type I interferon signaling through its strong complexes with nucleic acids. [27]

Accordingly, peptide-based strategies in psoriasis focus not on peptide replacement but on modulating LL-37–driven immune activation or developing peptide analogues capable of redirecting pathogenic innate immune signaling. Human evidence remains largely mechanistic and observational, supported by lesional expression studies and limited exploratory topical peptide investigations rather than robust interventional trials. [28] The translational challenge lies in the dual role of LL-37, which contributes both to host defense and autoimmune amplification, complicating therapeutic targeting without disrupting essential skin immune functions. [27,28]

Type 1 Diabetes (T1D)

Type 1 diabetes is caused by the immune-mediated destruction of pancreatic β cells driven primarily by autoreactive T cells. Consequently, vaccines have been developed that work on the principle of inducing antigen-specific tolerance by targeting insulin or GAD65 peptide epitopes in a selective way so that only the

pathogenic immune responses are modulated rather than broad immunosuppression. [29]

Multiple phase I/II clinical trials employing oral, nasal, and subcutaneous peptide delivery have demonstrated favorable safety profiles and variable immunologic effects, including altered antigen-specific T-cell responses and regulatory immune signatures. However, the consistency of β-cell function preservation or long-lasting disease progression prevention has not yet been reached, which reveals the translational limitations of using peptide-based tolerance induction in already existing T1D. [25,30]

In the case of autoimmune diseases like multiple sclerosis, rheumatoid arthritis, and type 1 diabetes, therapy with antigen-specific peptide has always been accompanied by immunologic activity and good safety levels, but the long-term clinical benefit has, to a great extent, been restricted by factors such as immune heterogeneity, epitope spreading, and the difficulty of establishing tolerance in a patient with already established chronic disease.

CROSS-CUTTING INSIGHTS FROM PEPTIDE-CENTRED EVIDENCE

As summarized in Table 1, therapeutic peptides across autoimmune diseases are increasingly characterized as agents that selectively modulate immune pathways rather than induce broad immunosuppression. A number of reviews affirm that the peptides often imitate the endogenous regulatory molecules, making the targeting of the immune signaling involved in autoimmunity possible. [29,31] Thymosin-α1 is specifically reported to promote T-cell maturation and immune homeostasis without evidence of generalized immune suppression in a review. [31]

Multiple studies mention that the immunoregulatory peptides influence the activities of the dendritic cells, the production of cytokines, and T-cell polarization, which distinguishes them mechanistically from the conventional immunosuppressive agents that target multiple immune compartments at the same time. [31]

The safety and tolerability of the peptides are our main points of focus from the previous literature. Several reviews, which give an overview of the preclinical models and early human studies, all point out that peptide-based interventions are mostly associated with mild and transient adverse events, very little evidence of cumulative toxicity, and thus they are treated as safe. The agents are claimed to have this profile due to being similar in structure to endogenous peptides, undergoing quick metabolic degradation, and being limited in terms of tissue accumulation. [20,32]

Several reviews conceptualise peptide therapies as agents capable of immune regulation rather than simple inflammatory suppression. Emerging peptide strategies are described as capable of down-regulating pathogenic immune responses while preserving broader immune function, particularly in the context of antigen-specific approaches. [9,33] The major translational limitation identified across several reviews is the absence of durable clinical outcome data, not the insufficient mechanistic understanding. [34]

Table 1. Cross-Disease Synthesis of Therapeutic Peptide Strategies in Autoimmune Disorders

Autoimmune disease	Dominant immune pathology	Representative peptides	Human evidence status	Key translational barrier
Multiple sclerosis	Antigen-driven CNS demyelination; autoreactive T cells	Myelin-derived peptides; altered peptide ligands; thymosin-α1	Phase I-II trials; pilot studies	HLA heterogeneity; epitope spreading
Rheumatoid arthritis	Synovial autoimmunity; proinflammatory	Citrullinated peptides; HSP60-derived APLs (CIGB-814)	Early-phase human trials	Limited phase III efficacy data

	cytokine signaling			
Systemic lupus erythematosus	Loss of immune tolerance; systemic immune dysregulation	Tolerogenic peptides; thymic peptides	Pilot and early-phase studies	Disease heterogeneity; variable organ involvement
Inflammatory bowel disease	Epithelial barrier dysfunction; mucosal inflammation	LL-37; KPV; BPC-157	Preclinical; limited exploratory human data	Lack of controlled clinical trials
Psoriasis	Innate immune amplification; IL-23/IL-17 axis	LL-37 modulating peptides; peptide analogues	Mechanistic and observational human evidence	Dual pathogenic and protective roles of LL-37
Type 1 diabetes	Immune-mediated β-cell destruction	Insulin peptides; GAD65 peptides	Phase I-II clinical trials	Lack of durable tolerance induction

PEPTIDES VS. CONVENTIONAL IMMUNOSUPPRESSANTS

Therapeutic peptides are discussed across multiple reviews as a class of agents increasingly explored for the treatment of immune-mediated and inflammatory diseases, with distinct structural and pharmacological properties compared with conventional small-molecule immunosuppressants. [35,36] These sources describe peptides as biologically active molecules that can interact with immune processes involved in disease pathogenesis.

Several reviews report that immunomodulatory peptides are capable of influencing immune responses through interactions with immune cells and signalling pathways, including effects on antigen-related immune mechanisms and cellular immune responses. [35,37] Thymic peptides and host-defence peptides are described as having immunoregulatory roles in both innate and adaptive immunity, based on experimental and early clinical observations. [31]

Conventional immunosuppressive therapies, including glucocorticoids, calcineurin inhibitors, and antimetabolites, are described in the literature as agents that suppress immune activity through broad inhibition of immune signalling pathways. Reviews discussing current autoimmune treatment strategies note that such agents are effective in controlling inflammation but are also associated with well-recognised adverse effects during prolonged use. [38,39]

With respect to safety, multiple analyses describe peptide-based therapeutics as generally demonstrating favourable tolerability profiles in preclinical studies and early clinical trials. These reviews attribute observed safety characteristics to properties such as peptide degradability and limited persistence in biological systems, while also emphasising that immunogenicity remains an important consideration in peptide drug development. [36,37] Early human studies of antigen-specific peptide-based interventions, particularly in autoimmune conditions such as type 1 diabetes, report acceptable safety and measurable immunological effects.[40]

Several reviews discuss peptide-based strategies in the context of immune tolerance and immune regulation, particularly approaches designed to target antigen-specific immune responses. These sources describe tolerance induction as a conceptual objective of peptide immunotherapy rather than an established clinical outcome, noting that consistent and durable tolerance has not yet been demonstrated across large patient populations. [33,41]

Across the reviewed literature, a consistent limitation highlighted for peptide-based therapeutics is the relative scarcity of long-term clinical outcome data. Reviews note that many studies remain early-phase, with small cohorts, short follow-up periods, and limited direct comparisons with established immunosuppressive therapies. [39,42]

Challenges related to peptide development are also discussed, including issues of molecular stability, delivery, formulation, and scalable manufacturing. Reviews addressing peptide production emphasise that these factors remain important considerations for clinical translation. [43,44]

In sum, therapeutic peptides represent a promising immunomodulatory strategy for autoimmunity, distinguished by their specificity, favourable safety, and potential to restore immune balance. However, their application remains at an earlier stage of clinical validation than conventional immunosuppressants, and significant translational hurdles remain before they can become widely adopted standard-of-care options.

LIMITATIONS AND GAPS

Peptide therapeutics have been extensively researched and studied for their immunomodulatory properties, but there are still some innate limitations that prevent their clinical application. Inherent susceptibility of peptides to enzymatic breakdown, along with poor in vivo stability, leads to very short plasma half-lives and very rapid elimination from the body after administration. [41,45]

Low oral bioavailability is still regarded as a major obstacle because peptides undergo rapid digestion in the GI tract and lack of permeability, which results in most peptides being developed for injection and non-invasive delivery techniques still being in the experimental stage. [45,46] Apart from these issues with drugs and delivery, there are challenges associated with peptide formulation and the need for analytical characterization that must be taken into account in the developmental process, influencing the pathway of drug translational studies. [41]

The clinical use of peptide immunotherapy is mainly restricted to the studies of early-phase or small cohorts, and the data on long-term outcomes are still very limited, thus requiring controlled trials to prove safety and prolonged efficacy in larger patient populations. [45] All these limitations, when viewed together, not only indicate the current stage but also point out the main areas in which further research and advanced technology are required for the development of peptide therapeutics.

FUTURE DIRECTIONS

Personalized approaches are increasingly discussed in the peptide immunotherapy literature as a potential strategy to improve translational outcomes in autoimmune disease. [42] Several reviews and early clinical studies indicate that immune responses to antigen-specific peptides vary across patients, reflecting differences in HLA background, immune activation state, and disease stage. [40] These findings have led researchers to suggest that future studies may benefit from incorporating immune phenotyping, biomarker-based stratification, or adaptive trial designs. [42]

The literature also discusses multi-epitope or multi-peptide strategies as a potential approach to address immune heterogeneity. [44] Reviews on peptide vaccine and tolerance describe experimental designs in which multiple antigenic peptides are combined to target broader immune repertoires or reduce the impact of epitope variability. [37,44] While these approaches have shown mechanistic promise in preclinical systems and early translational work, human clinical evidence remains limited, and scientists emphasize the need for careful evaluation of immune interactions, dosing, and safety when combining peptide components. [37]

Multiple reviews describe ongoing efforts to enhance peptide stability, protect against proteolytic degradation, and improve tissue targeting through formulation strategies such as encapsulation, chemical modification, and controlled-release systems. [43,47] Additional analyses discuss receptor-mediated transport, depot systems, and targeted delivery approaches as potential methods to improve peptide

bioavailability and pharmacokinetic consistency. [41]

Evidence linking microbiome composition and immune homeostasis has led researchers to propose that future peptide-based interventions may need to be evaluated alongside factors such as diet or microbiome-modulating strategies, particularly in diseases involving mucosal immune dysfunction. [20,25] The literature consistently emphasizes the need for rigorously designed trials to distinguish additive or synergistic effects from background variability. [20]

Across reviews, a consistent conclusion is that progress in peptide therapeutics will depend on coordinated advances in peptide engineering, delivery technologies, biomarker development, and clinical trial methodology. [39] Multiple sources emphasize that well-powered, long-duration, multicenter studies with stratified enrollment and standardized clinical endpoints are required before peptide-based immunomodulation can be considered a validated therapeutic strategy in autoimmune disease. [36,39]

CONCLUSION

Therapeutic peptides have modernized the approach to immunosuppression by selectively modulating the immune system's activities, such as enhanced dendritic cell, T-cell polarization, cytokine signaling, with the advantage of limited toxicity and rapid clearance of the drug. Their efficacy in treating autoimmune diseases has yet to be fully realized since very small sample sizes and short durations of early-phase clinical trials pose a problem, in addition to the issues of peptide stability and delivery. The primary limitation of peptide immunotherapy was not mechanistic failure but insufficient clinical trial design and execution. Technological advancements, patient stratification, and long-term studies are prerequisites for the wider use of peptide therapeutics in the clinic.

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