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Autoimmunity-How Genes, Infections and Injury Trigger the Body to Attack Itself: A Structured Narrative Review

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ABSTRACT

In autoimmune disease the immune system, which normally protects the body, attacks the body's own tissues. These diseases are chronic, often disabling, and commonly seen in rehabilitation practice. Their causes are not single but layered, and the evidence is spread across genetics, microbiology and pathology. To synthesise current evidence on how genetic susceptibility, infections and tissue injury trigger autoimmunity, and to present it as a simple multifactorial model that can be used in teaching and clinical education. A structured narrative review was carried out. PubMed/MEDLINE, Scopus and Google Scholar were searched, along with standard pathology and immunology textbooks, using predefined search terms and inclusion criteria. Selected studies were screened, appraised for quality and synthesised thematically under genetic, infectious, injury-related and other contributing factors. Genetic susceptibility, especially variation in the HLA region, increases risk but does not cause disease on its own. Infections can trigger autoimmunity through molecular mimicry, bystander activation and epitope spreading. Injury or surgery can release sequestered antigens to which tolerance was never established. Sex hormones, drugs, smoking and other environmental factors modify the risk, and weak regulatory control allows self-reactive cells to persist. Autoimmunity is multifactorial. A

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susceptible genetic background, an environmental trigger and a failure of regulation usually act together. This layered view explains familial clustering, post-infectious and post-traumatic onset, and the female predominance seen in many diseases.

1. Introduction

Every day the immune system meets an enormous number of foreign molecules and also handles the body's own proteins, which far outnumber them. Its most important skill is not attack but discrimination: it must respond strongly to a virus or bacterium and stay quiet towards the person's own cells. When this discrimination fails and the immune response is directed against self, the result is an autoimmune disease [1].

Autoimmune diseases are a varied group. Some are organ-specific, such as type 1 diabetes, Hashimoto's thyroiditis and multiple sclerosis. Others are systemic, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. Taken together they affect a substantial share of the population, and many are chronic and need lifelong treatment [2,3]. Several of them affect joints, muscles and nerves, which makes them directly relevant to physiotherapists and other rehabilitation professionals [4].

A natural question for any student is why the body begins to attack itself. We do not have one answer. Research over several decades points to a combination of inherited susceptibility, environmental triggers and failing regulation. This paper groups the evidence under three headings that are easy to remember and teach: genes, infections and injury, with hormones and other environmental influences as modifiers.

Objectives. (1) To describe how self-tolerance is established and how it fails. (2) To summarise the evidence for genetic, infectious and injury-related triggers of autoimmunity. (3) To integrate these into a single multifactorial model. (4) To outline the relevance of this model for health professions education.

2. Research methodology

2.1 Study design

This is a structured narrative review. A narrative design was chosen because the aim was to explain mechanisms across several disciplines, which does not fit the narrow question and pooled analysis of a systematic review or meta-analysis. To limit bias, the review followed a predefined protocol for searching, selection and appraisal, drawing on published guidance for narrative reviews [5], and the SANRA criteria

were used as a quality checklist for the review itself [6]. The flow of records is reported in the manner recommended by the PRISMA 2020 statement [7], although this is not a formal systematic review.

2.2 Data sources and search strategy

Three electronic databases were searched: PubMed/MEDLINE, Scopus and Google Scholar. Standard textbooks of pathology and immunology were also consulted [4,36,37]. The search covered the period from January 2000 to October 2026, and earlier landmark papers were added where they were historically important for the concepts discussed. Reference lists of key articles were hand-searched for further sources.

Table 1. Search strategy

Concept	Search terms (combined with AND between concepts, OR within concepts)
Autoimmunity	autoimmunity OR "autoimmune disease" OR "loss of self-tolerance" OR autoantibod*
Genetic factors	HLA OR "human leukocyte antigen" OR "genetic susceptibility" OR "twin study" OR "familial clustering"
Infection	infection OR "molecular mimicry" OR "bystander activation" OR "epitope spreading"
Injury	"sequestered antigen" OR "immune privilege" OR trauma OR "tissue injury"
Modifiers	"sex hormones" OR smoking OR environment OR "regulatory T cells"

2.3 Eligibility criteria

Inclusion: peer-reviewed review articles, original studies, consensus statements and major textbooks; written in English; addressing mechanisms, risk factors or epidemiology of autoimmune disease in humans, including supporting experimental work.

Exclusion: conference abstracts without full text; case reports used alone to support a mechanism; articles dealing only with drug treatment or clinical trials of therapy; non-English papers without an available translation; and duplicates.

2.4 Study selection and data extraction

Records from all sources were combined and duplicates removed. Titles and abstracts were screened against the eligibility criteria, and the full text of potentially relevant articles was read. From each included source the following were extracted: author and year, type of study, disease or condition studied, trigger or mechanism examined, and the main finding. A total of [n] records were identified, [n] remained after duplicates were removed, [n] full texts were assessed, and [n] sources were included in the final synthesis.

2.5 Quality appraisal and synthesis

Preference was given to high-quality sources such as large cohort studies, genetic association studies, well-cited reviews and standard textbooks. The strength of each association was judged by the consistency of findings across studies and by whether a plausible biological mechanism had been demonstrated. Findings were then grouped thematically into tolerance, genetic factors, infections, injury and sequestered antigens, and other modifiers, and combined into the integrated model described in Section 3.6.

2.6 Ethical considerations

This review is based entirely on published literature and involved no human participants, patient data or animal experiments. Formal ethical clearance was therefore not required. All sources are acknowledged in the reference list.

3. Results: synthesis of the evidence

3.1 Self-tolerance and how it fails

To understand autoimmunity, it helps to know how the immune system normally learns what to ignore. This learning is called **immune tolerance** [8,9].

Central tolerance develops in the primary lymphoid organs. As T cells mature in the thymus, those that react strongly to self-antigens are eliminated or diverted. A similar process occurs for B cells in the bone marrow. This early education removes most dangerous self-reactive cells.

Peripheral tolerance works after cells have left these organs, because central tolerance is never perfect. Self-reactive cells that escape may be made unresponsive (anergy), deleted, or restrained by regulatory T cells, which actively suppress other lymphocytes [9,10].

Autoimmunity develops when these safeguards are overcome. A few self-reactive cells exist in almost every healthy person, and disease appears when such cells are activated and sustained. The tissue damage that follows is caused by autoantibodies, immune complexes, or cytotoxic and inflammatory T cells, depending on the disease. Criteria for proving that a disease is truly autoimmune were first proposed by Witebsky and colleagues in 1957 and were later revised: they include demonstrating an immune response to a self-antigen and reproducing the disease in experimental animals [11,12].

3.2 Genetic susceptibility

Evidence from families and twins: Autoimmune diseases tend to run in families, and relatives of patients carry a higher risk than the general population. Identical twins are more often both affected than non-identical twins, which points to a genetic contribution, but concordance is well below 100 per cent. If genes were the whole story, identical twins would always share the disease. They do not, and that tells us the environment matters too [1,13].

The HLA genes: The strongest and best-studied genetic link lies in the **human leukocyte antigen (HLA)** region, the human form of the major histocompatibility complex on chromosome 6. HLA molecules sit on cell surfaces and present small fragments of proteins (peptides) to T cells. Class I molecules (HLA-A, B, C) present to CD8-positive cytotoxic T cells, and class II molecules (HLA-DR, DP, DQ) present to CD4-positive helper T cells. Because these molecules decide which peptides are shown to T cells, small differences between them can change what the immune system notices [14,15].

Table 2. Classic HLA associations

HLA type	Associated disease	Notes
HLA-B27	Ankylosing spondylitis	Carried by the large majority of patients, but also by a small percentage of healthy people [16]
HLA-DR4 (and related “shared epitope” alleles)	Rheumatoid arthritis	Carriers have a several-fold higher risk [17]
HLA-DR3	SLE, myasthenia gravis, type 1 diabetes	Associated with several autoimmune conditions [15]
HLA-DR2	Multiple sclerosis	Increased risk in carriers [14]

The link between HLA-B27 and ankylosing spondylitis has been recognised for decades and remains one of the strongest known associations in medicine [16]. In rheumatoid arthritis, the "shared epitope" hypothesis proposed that several DR alleles carry a similar stretch of amino acids in the peptide-binding groove, which may explain why different alleles confer similar risk [17].

Why would an HLA type raise risk? The mechanisms are still debated, but three ideas are widely discussed. First, some HLA molecules may present self-peptides more efficiently and so activate self-reactive T cells. Second, they may present microbial peptides that resemble self. Third, certain HLA types may shape T cell selection in the thymus in a way that lets self-reactive cells survive [14,15].

Beyond HLA: Genome-wide studies have found many other susceptibility genes, each adding a small effect, including genes that control immune signalling and regulatory T cell function. Epigenetic changes, which alter gene activity without changing the DNA sequence, are also under study and may link environmental exposures to disease [18].

An important caution: HLA association is a **risk factor, not a diagnosis**. Most people who carry HLA-B27 or HLA-DR4 never develop the related disease, and HLA typing alone cannot confirm or exclude it. Diagnosis rests on clinical features, imaging and laboratory tests.

3.3 Infections as triggers

The link between infection and autoimmunity is old and persuasive. Rheumatic fever after streptococcal throat infection and Guillain-Barré syndrome after certain gastrointestinal or respiratory infections are well-known examples [23,24]. Infections may act through several routes [19,20,27].

Molecular mimicry: Sometimes a microbial protein looks, at the level of a short peptide, similar to a self-protein. An immune response that is correct for the microbe can then cross-react with host tissue. The idea has experimental support, for example in studies where viral peptides activated T cell clones that also recognised myelin basic protein [21,22]. In rheumatic heart disease, antibodies to streptococcal components are thought to cross-react with cardiac tissue [23].

Bystander activation: During an infection, inflammation raises the level of co-stimulatory molecules and cytokines in the tissues. In this inflamed setting, self-reactive T cells that happen to be nearby may be activated even though they do not recognise the microbe at all. Infection can also damage tissue and release hidden antigens [20].

Epitope spreading: Once tissue damage begins, the immune response can widen to include additional self-antigens that were not part of the original attack. This helps explain why autoimmune diseases often progress and flare over time [25].

A recent example: The link between Epstein-Barr virus infection and multiple sclerosis has drawn renewed attention. A large study of military personnel found that the risk of multiple sclerosis rose markedly after infection with the virus, which strengthened the case that it is a significant contributor [26]. As with the other examples, however, most people infected with the virus do not develop the disease.

3.4 Tissue injury and sequestered antigens

Some self-antigens are normally hidden from the immune system behind anatomical barriers. Examples include proteins of the eye lens, sperm, and thyroglobulin inside thyroid follicles. Because lymphocytes never meet these antigens during their development, tolerance is not established, and self-reactive cells against them may remain in the body [28].

If injury, surgery or infection breaks the barrier, the antigen is released and is recognised as foreign. Well-described examples include:

- **Eye:** injury to one eye can cause inflammation in the other (sympathetic ophthalmia), and lens protein released after trauma or cataract surgery can cause lens-induced uveitis [28].
- **Testis:** anti-sperm antibodies may appear after vasectomy, testicular trauma or mumps orchitis, and can contribute to infertility.
- **Thyroid:** release of thyroglobulin is linked to autoimmune thyroiditis.
- **Heart:** pericarditis that appears weeks after a myocardial infarction (Dressler syndrome) is attributed to an immune response to released cardiac antigens [29].

This mechanism explains why autoimmunity can follow trauma or surgery and not only infection. The antigen is not truly foreign. It only appears so because the immune system was never taught to tolerate it. Most people who suffer such injuries do not go on to develop autoimmune disease.

3.5 Other contributing factors

Sex hormones: Many autoimmune diseases are considerably more common in women, including SLE, Hashimoto's thyroiditis and rheumatoid arthritis. Oestrogen and other sex hormones influence immune cell

behaviour, and genes on the X chromosome may also play a part, although the full explanation is not yet clear [30,31,32].

Drugs: Some drugs can induce lupus-like syndromes, which usually improve after the drug is stopped. This shows that external agents can directly disturb immune regulation [33].

Environment and lifestyle: Smoking, ultraviolet light, certain chemicals, diet, stress and changes in the gut microbiome have all been proposed as influences. Evidence is stronger for some, such as smoking in rheumatoid arthritis, than for others [33,34].

Failure of regulatory mechanisms: Defects in regulatory T cells or in the signals that normally switch immune responses off can allow self-reactive cells to persist [10].

Table 3. Summary of mechanisms and evidence

Factor	How it contributes	Examples	Key sources
HLA genes	Alter which peptides are shown to T cells	HLA-B27 and ankylosing spondylitis; HLA-DR4 and rheumatoid arthritis	[14-17]
Molecular mimicry	Microbial peptide resembles self	Rheumatic heart disease; viral and myelin peptides	[21-23]
Bystander activation	Inflammation activates nearby self-reactive cells	Post-infectious autoimmunity	[19,20]
Epitope spreading	Response widens to new self-antigens	Progression and flares	[25]
Sequestered antigens	Hidden antigens released after injury	Sympathetic ophthalmia; Dressler syndrome	[28,29]
Sex hormones	Modify immune cell behavior	Female predominance in SLE	[30-32]
Environment	Smoking and other exposures	Smoking and rheumatoid arthritis	[33,34]
Loss of	Weak suppression of self-	Reduced regulatory T cell function	[9,10]

Factor	How it contributes	Examples	Key sources
regulation	reactive cells		

3.6 An integrated multifactorial model

It is tempting to look for one cause, but the evidence supports a layered model.

1. **Susceptibility:** inherited HLA and non-HLA genes make some people more prone.
2. **Trigger:** an infection, injury, drug or other exposure activates self-reactive cells.
3. **Breakdown of control:** tolerance mechanisms fail to restrain these cells.
4. **Amplification:** inflammation, epitope spreading and ongoing antigen supply sustain the response.
5. **Tissue damage:** autoantibodies, immune complexes or T cells injure the target tissue, leading to clinical disease.

This model explains several familiar features at once: why disease clusters in families but is not inevitable, why symptoms may begin after an infection or injury, why the same trigger harms only a few people, and why disease tends to follow a relapsing course.

4. Discussion

The evidence reviewed here shows that autoimmunity is best understood as the outcome of several interacting factors and not of a single defect. Genetic susceptibility sets the stage, but twin data show that genes alone cannot account for disease [1,13]. Environmental triggers such as infection and injury then supply the spark, and the strength of the evidence varies. For some associations, such as HLA-B27 with ankylosing spondylitis, the link is very strong [16]. For others, such as the role of the gut microbiome, the evidence is still emerging [33].

Relevance to health professions education: For physiotherapists and other allied health workers, understanding these mechanisms has practical value. Many patients seen in rehabilitation have autoimmune conditions that affect joints, muscles and nerves, including rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis and myasthenia gravis. Knowing that these are chronic, relapsing and multifactorial diseases supports better patient education, realistic expectations about outcomes, and sensitivity to the effects of fatigue and flares on exercise tolerance. A clear grasp of the mechanisms also helps students avoid

common misunderstandings, such as treating an HLA association as a diagnosis, or assuming that a trigger always leads to disease. Teaching the layered model of susceptibility, trigger, loss of control and damage gives students a framework they can apply to any autoimmune disease they meet later.

Implications for treatment and prevention: Understanding triggers has implications beyond teaching. Treatment of autoimmune disease has moved towards targeting specific immune pathways, and continued research on mechanisms is the basis for these advances [35]. Because most people with a risk factor never develop disease, identifying who is truly at risk, and which exposures can be modified, remains an important research goal.

Strengths and limitations: The strengths of this review are its predefined search strategy, explicit eligibility criteria and its integration of genetic, infectious and injury-related evidence in one framework. Its limitations should also be stated. It is a narrative and not a systematic review, so it cannot give pooled estimates of risk. It was limited to English-language sources and to three databases and may have missed relevant studies. It does not cover every autoimmune disease or the details of treatment. Research in this field moves quickly, particularly regarding the microbiome, epigenetics and newer immune therapies, and readers should consult current literature for the latest findings.

Future directions: Useful areas for further work include large population studies of how genes and environment interact, studies from Indian populations, where HLA frequencies and exposures differ from those in the Western cohorts that dominate the literature, and educational research on how best to teach these mechanisms to allied health students.

5. Conclusion

Autoimmunity is best understood as a failure of the body's discrimination between self and non-self. Genetic susceptibility, notably HLA type, sets the stage. Infections and tissue injury can then supply the trigger, either by resembling self-antigens or by exposing antigens that were hidden. Hormones, drugs and the wider environment modify the risk, and weakened regulatory control allows the process to continue. No single factor is sufficient, and most people with a risk gene or a trigger never develop disease. Teaching this multifactorial picture gives students and clinicians a more accurate and more useful understanding of why autoimmune diseases occur and why they vary so much between individuals.

Declarations

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References

1. Davidson A, Diamond B. Autoimmune diseases. N Engl J Med. 2001;345(5):340-350.
2. Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. J Intern Med. 2015;278(4):369-395.
3. Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. J Autoimmun. 2009;33(3-4):197-207.
4. Mohan H. Textbook of Pathology. Jaypee Brothers Medical Publishers; chapter on immunopathology and autoimmune diseases.
5. Green BN, Johnson CD, Adams A. Writing narrative literature reviews for peer-reviewed journals: secrets of the trade. J Chiropr Med. 2006;5(3):101-117.
6. Baethge C, Goldbeck-Wood S, Mertens S. SANRA: a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019;4:5.
7. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
8. Kamradt T, Mitchison NA. Tolerance and autoimmunity. N Engl J Med. 2001;344(9):655-664.
9. Goodnow CC, Sprent J, Fazekas de St Groth B, Vinuesa CG. Cellular and genetic mechanisms of self tolerance and autoimmunity. Nature. 2005;435(7042):590-597.
10. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. Cell. 2008;133(5):775-787.
11. Witebsky E, Rose NR, Terplan K, Paine JR, Egan RW. Chronic thyroiditis and autoimmunization. JAMA. 1957;164(13):1439-1447.
12. Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). Immunol Today. 1993;14(9):426-430.

13. Selmi C, Lu Q, Humble MC. Heritability versus the role of the environment in autoimmunity. J Autoimmun. 2012;39(4):249-252.

14. Trowsdale J, Knight JC. Major histocompatibility complex genomics and human disease. Annu Rev Genomics Hum Genet. 2013;14:301-323.

15. Gough SCL, Simmonds MJ. The HLA region and autoimmune disease: associations and mechanisms of action. Curr Genomics. 2007;8(7):453-465.

16. Brown MA, Kenna T, Wordsworth BP. Genetics of ankylosing spondylitis: insights into pathogenesis. Nat Rev Rheumatol. 2016;12(2):81-91.

17. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. Arthritis Rheum. 1987;30(11):1205-1213.

18. Hewagama A, Richardson B. The genetics and epigenetics of autoimmune diseases. J Autoimmun. 2009;33(1):3-11.

19. Ercolini AM, Miller SD. The role of infections in autoimmune disease. Clin Exp Immunol. 2009;155(1):1-15.

20. Fujinami RS, von Herrath MG, Christen U, Whitton JL. Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. Clin Microbiol Rev. 2006;19(1):80-94.

21. Wucherpfennig KW, Strominger JL. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell. 1995;80(5):695-705.

22. Cusick MF, Libbey JE, Fujinami RS. Molecular mimicry as a mechanism of autoimmune disease. Clin Rev Allergy Immunol. 2012;42(1):102-111.

23. Cunningham MW. Pathogenesis of group A streptococcal infections. Clin Microbiol Rev. 2000;13(3):470-511.

24. Yuki N, Hartung HP. Guillain-Barré syndrome. N Engl J Med. 2012;366(24):2294-2304.

25. Vanderlugt CL, Miller SD. Epitope spreading in immune-mediated diseases: implications for immunotherapy. Nat Rev Immunol. 2002;2(2):85-95.

26. Bjornevik K, Cortese M, Healy BC, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science. 2022;375(6578):296-301.

27. Kivity S, Agmon-Levin N, Blank M, Shoenfeld Y. Infections and autoimmunity: friends or foes? Trends Immunol. 2009;30(8):409-414.

28. Streilein JW. Ocular immune privilege: therapeutic opportunities from an experiment of nature. Nat Rev Immunol. 2003;3(11):879-889.

29. Dressler W. A post-myocardial-infarction syndrome: preliminary report of a complication resembling idiopathic, recurrent, benign pericarditis. JAMA. 1956;160(16):1379-1383.

30. Fairweather D, Rose NR. Women and autoimmune diseases. Emerg Infect Dis. 2004;10(11):2005-2011.

31. Fairweather D, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. Am J Pathol. 2008;173(3):600-609.

32. Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol. 2014;35(3):347-369.

33. Miller FW, Alfredsson L, Costenbader KH, et al. Epidemiology of environmental exposures and human autoimmune diseases: findings from a National Institute of Environmental Health Sciences expert panel workshop. J Autoimmun. 2012;39(4):259-271.

34. Costenbader KH, Karlson EW. Cigarette smoking and autoimmune disease: what can we learn from epidemiology? Lupus. 2006;15(11):737-745.

35. Fugger L, Jensen LT, Rossjohn J. Challenges, progress, and prospects of developing therapies to treat autoimmune diseases. Cell. 2020;181(1):63-80.

36. Kumar V, Abbas AK, Aster JC. Robbins and Cotran Pathologic Basis of Disease. Elsevier; chapter on diseases of the immune system.

37. Abbas AK, Lichtman AH, Pillai S. Cellular and Molecular Immunology. Elsevier; chapters on immunological tolerance and autoimmunity.