**Patologie Autoimmuni aa 2023-2024**

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Klein L et al. (2014) Positive and negative selection of T cell repertoire: what thymocytes see (and don't see) Nature Rev. Immunol. 14:377

Takahama Y. (2012) β5t-containing thymoproteasome: specific expression in thymic cortical epithelial cells and role in positive selection of CD8+ T cells. Current Opinion in Immunology. 24:92.

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Sakagushi S et al. (2008) Regulatory T cells and immune tolerance. Cell 133:775.

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Ellebrecht CT, et al. (2019) On the mark: genetically engineered immunotherapies for autoimmunity. Curr Opin Immunol. 61:69

Science. 2020 Sep 25;369:eaay4014.

doi: 10.1126/science.aay4014.

# The science and medicine of human immunology

## Pulendran B, Davis MM

## Abstract

Although the development of effective vaccines has saved countless lives from infectious diseases, the basic workings of the human immune system are complex and have required the development of animal models, such as inbred mice, to define mechanisms of immunity. More recently, new strategies and technologies have been developed to directly explore the human immune system with unprecedented precision. We discuss how these approaches are advancing our mechanistic understanding of human immunology and are facilitating the development of vaccines and therapeutics for infection, autoimmune diseases, and cancer.

[Nat Rev Drug Discov.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Miossec+P+Targeting+IL-17+and+TH17+cells+in+chronic+inflammation) 2012 Oct;11(10):763-76. doi: 10.1038/nrd3794.

# Targeting IL-17 and TH17 cells in chronic inflammation.

[Miossec P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Miossec%20P%5BAuthor%5D&cauthor=true&cauthor_uid=23023676)1, [Kolls JK](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kolls%20JK%5BAuthor%5D&cauthor=true&cauthor_uid=23023676).

### Abstract

The key role of interleukin-17 (IL-17) and T helper 17 (T(H)17) cells in tissue inflammation, autoimmunity and host defence led to the experimental targeting of these molecules in mouse models of diseases as well as in clinical settings. Moreover, the demonstration that IL-17 and T(H)17 cells contribute to local and systemic aspects of disease pathogenesis, as well as the finding that the IL-17-T(H)17 cell pathway is regulated by IL-23, prompted the identification of inhibitors. These inhibitors include biotechnology products that target IL-23 as well as the leading member of the IL-17 family, IL-17A, and one of its receptors, IL-17 receptor A. Several clinical trials of these inhibitors are underway, and positive results have been obtained in psoriasis, rheumatoid arthritis and ankylosing spondylitis. This Review focuses on the current knowledge of the IL-17-T(H)17 cell pathway to better understand the positive as well as potential negative consequences of targeting them.

[Semin Immunol.](http://www.ncbi.nlm.nih.gov/pubmed/?term=Geginat+J++The+CD4-centered+universe+of+human+T+cell+subsets.) 2013 Nov 15;25(4):252-62. doi: 10.1016/j.smim.2013.10.012. Epub 2013 Nov 1.

**The CD4-centered universe of human T cell subsets.**

[Geginat J](http://www.ncbi.nlm.nih.gov/pubmed?term=Geginat%20J%5BAuthor%5D&cauthor=true&cauthor_uid=24183700), [Paroni M](http://www.ncbi.nlm.nih.gov/pubmed?term=Paroni%20M%5BAuthor%5D&cauthor=true&cauthor_uid=24183700), [Facciotti F](http://www.ncbi.nlm.nih.gov/pubmed?term=Facciotti%20F%5BAuthor%5D&cauthor=true&cauthor_uid=24183700), [Gruarin P](http://www.ncbi.nlm.nih.gov/pubmed?term=Gruarin%20P%5BAuthor%5D&cauthor=true&cauthor_uid=24183700), [Kastirr I](http://www.ncbi.nlm.nih.gov/pubmed?term=Kastirr%20I%5BAuthor%5D&cauthor=true&cauthor_uid=24183700), [Caprioli F](http://www.ncbi.nlm.nih.gov/pubmed?term=Caprioli%20F%5BAuthor%5D&cauthor=true&cauthor_uid=24183700), [Pagani M](http://www.ncbi.nlm.nih.gov/pubmed?term=Pagani%20M%5BAuthor%5D&cauthor=true&cauthor_uid=24183700), [Abrignani S](http://www.ncbi.nlm.nih.gov/pubmed?term=Abrignani%20S%5BAuthor%5D&cauthor=true&cauthor_uid=24183700).

**Abstract**

Humans are continuously exposed to a high number of diverse pathogens that induce different types of immune responses. Primary pathogen-specific immune responses generate multiple subsets of memory T cells, which provide protection against secondary infections. In recent years, several novel T cell subsets have been identified and have significantly broadened our knowledge about T cell differentiation and the regulation of immune responses. At the same time the rapidly growing number of incompletely characterized T cell subsets has also generated some controversies. We therefore review here the current knowledge on features and functions of human α/β T cell subsets, focusing on CD4(+) T cells classified according to cytokine production and tissue localization. The principal helper and regulatory T cell subsets can be identified by a limited number of relevant surface markers, which are an integral part of the T cell differentiation programs because they are directly induced by the relevant lineage-defining transcription factors. In vivo occurring human T cell subsets can thus be purified directly ex vivo from relevant tissues for molecular and functional studies, and represent not only an ideal model to study T cell differentiation, but they also offer important clinical opportunities

Curr Opin Immunol 61, 1-9 Dec 2019

#  Spatial and Functional Heterogeneity of Follicular Helper T Cells in Autoimmunity

[Abhinav Seth](https://pubmed.ncbi.nlm.nih.gov/?term=Seth+A&cauthor_id=31374450) [1](https://pubmed.ncbi.nlm.nih.gov/31374450-spatial-and-functional-heterogeneity-of-follicular-helper-t-cells-in-autoimmunity/?from_single_result=seth+a+spatial+and+functional+heterogeneity+review#affiliation-1) , [Joe Craft](https://pubmed.ncbi.nlm.nih.gov/?term=Craft+J&cauthor_id=31374450) [2](https://pubmed.ncbi.nlm.nih.gov/31374450-spatial-and-functional-heterogeneity-of-follicular-helper-t-cells-in-autoimmunity/?from_single_result=seth+a+spatial+and+functional+heterogeneity+review#affiliation-2)

## Abstract

Follicular helper T cells provide signals that promote B cell development, proliferation, and production of affinity matured and appropriately isotype switched antibodies. In addition to their classical locations within B cell follicles and germinal centers therein, B cell helper T cells are also found in extrafollicular spaces - either in secondary lymphoid or non-lymphoid tissues. Both follicular and extrafollicular T helper cells drive autoantibody-mediated autoimmunity. Interfering with B cell help provided by T cells can ameliorate autoimmune disease in animal models and human patients. The next frontier in Tfh cell biology will be identification of Tfh cell-specific pathogenic changes in autoimmunity and exploiting them for therapeutic purposes.

Nat Immunol., 19 (7), 674-684 Jul 2018

**Approaches and Advances in the Genetic Causes of Autoimmune Disease and Their Implications**

[Jamie R J Inshaw](https://pubmed.ncbi.nlm.nih.gov/?term=Inshaw+JRJ&cauthor_id=29925982) [1](https://pubmed.ncbi.nlm.nih.gov/29925982-approaches-and-advances-in-the-genetic-causes-of-autoimmune-disease-and-their-implications/?from_term=Approaches+and+advances+in+the+genetic+causes+of+autoimmune+disease+and+their+implications&from_pos=1#affiliation-1) , [Antony J Cutler](https://pubmed.ncbi.nlm.nih.gov/?term=Cutler+AJ&cauthor_id=29925982) [1](https://pubmed.ncbi.nlm.nih.gov/29925982-approaches-and-advances-in-the-genetic-causes-of-autoimmune-disease-and-their-implications/?from_term=Approaches+and+advances+in+the+genetic+causes+of+autoimmune+disease+and+their+implications&from_pos=1#affiliation-1) , [Oliver S Burren](https://pubmed.ncbi.nlm.nih.gov/?term=Burren+OS&cauthor_id=29925982) [2](https://pubmed.ncbi.nlm.nih.gov/29925982-approaches-and-advances-in-the-genetic-causes-of-autoimmune-disease-and-their-implications/?from_term=Approaches+and+advances+in+the+genetic+causes+of+autoimmune+disease+and+their+implications&from_pos=1#affiliation-2) , [M Irina Stefana](https://pubmed.ncbi.nlm.nih.gov/?term=Stefana+MI&cauthor_id=29925982) [1](https://pubmed.ncbi.nlm.nih.gov/29925982-approaches-and-advances-in-the-genetic-causes-of-autoimmune-disease-and-their-implications/?from_term=Approaches+and+advances+in+the+genetic+causes+of+autoimmune+disease+and+their+implications&from_pos=1#affiliation-1) , [John A Todd](https://pubmed.ncbi.nlm.nih.gov/?term=Todd+JA&cauthor_id=29925982) [3](https://pubmed.ncbi.nlm.nih.gov/29925982-approaches-and-advances-in-the-genetic-causes-of-autoimmune-disease-and-their-implications/?from_term=Approaches+and+advances+in+the+genetic+causes+of+autoimmune+disease+and+their+implications&from_pos=1#affiliation-3)

**Abstract**

Genome-wide association studies are transformative in revealing the polygenetic basis of common diseases, with autoimmune diseases leading the charge. Although the field is just over 10 years old, advances in understanding the underlying mechanistic pathways of these conditions, which result from a dense multifactorial blend of genetic, developmental and environmental factors, have already been informative, including insights into therapeutic possibilities. Nevertheless, the challenge of identifying the actual causal genes and pathways and their biological effects on altering disease risk remains for many identified susceptibility regions. It is this fundamental knowledge that will underpin the revolution in patient stratification, the discovery of therapeutic targets and clinical trial design in the next 20 years. Here we outline recent advances in analytical and phenotyping approaches and the emergence of large cohorts with standardized gene-expression data and other phenotypic data that are fueling a bounty of discovery and improved understanding of human physiology.

[Trends Immunol.](https://www.ncbi.nlm.nih.gov/pubmed/23031829) 2013 Jan;34(1):22-6. doi: 10.1016/j.it.2012.09.001. Epub 2012 Sep 29.

# Immune-mediated disease genetics: the shared basis of pathogenesis.

[Cotsapas C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cotsapas%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23031829)1, [Hafler DA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hafler%20DA%5BAuthor%5D&cauthor=true&cauthor_uid=23031829).

### Abstract

Recent genetic studies in multiple autoimmune and inflammatory diseases have identified hundreds of genomic loci harboring risk variants. These variants are shared between diseases at unexpectedly high rates, providing a molecular basis for the shared pathogenesis of immune-mediated disease. If properly used, these results could allow us to identify specific pathways underlying disease; explain disease heterogeneity by grouping patients by molecular causes rather than overall symptomatology; and develop more rational approaches to diagnosis and therapy targeting these molecular defects. Here we review the current state of play in the genetics of immune-mediated disease, evidence for this sharing and how this new knowledge can lead to medically actionable discoveries of pathobiology.

[J Autoimmun.](http://www.ncbi.nlm.nih.gov/pubmed/26343334) 2015 Nov;64:1-12. doi: 10.1016/j.jaut.2015.08.015. Epub 2015 Sep 4.

# The genetics of human autoimmune disease: A perspective on progress in the field and future directions.

[Seldin MF](http://www.ncbi.nlm.nih.gov/pubmed/?term=Seldin%20MF%5BAuthor%5D&cauthor=true&cauthor_uid=26343334)1.

### Abstract

Progress in defining the genetics of autoimmune disease has been dramatically enhanced by large scale genetic studies. Genome-wide approaches, examining hundreds or for some diseases thousands of cases and controls, have been implemented using high throughput genotyping and appropriate algorithms to provide a wealth of data over the last decade. These studies have identified hundreds of non-HLA loci as well as further defining HLA variations that predispose to different autoimmune diseases. These studies to identify genetic risk loci are also complemented by progress in gene expression studies including definition of expression quantitative trait loci (eQTL), various alterations in chromatin structure including histone marks, DNase I sensitivity, repressed chromatin regions as well as transcript factor binding sites. Integration of this information can partially explain why particular variations can alter proclivity to autoimmune phenotypes. Despite our incomplete knowledge base with only partial definition of hereditary factors and possible functional connections, this progress has and will continue to facilitate a better understanding of critical pathways and critical changes in immunoregulation. Advances in defining and understanding functional variants potentially can lead to both novel therapeutics and personalized medicine in which therapeutic approaches are chosen based on particular molecular phenotypes and genomic alterations.

Curr Opin Immunol 37, 28-33 Dec 2015

#  Identifying Genetic Determinants of Autoimmunity and Immune Dysregulation

[Carrie L Lucas](https://pubmed.ncbi.nlm.nih.gov/?term=Lucas+CL&cauthor_id=26433354) [1](https://pubmed.ncbi.nlm.nih.gov/26433354-identifying-genetic-determinants-of-autoimmunity-and-immune-dysregulation/?from_single_result=lucas+cl+determinants+of+autoimmunity+review#affiliation-1) , [Michael J Lenardo](https://pubmed.ncbi.nlm.nih.gov/?term=Lenardo+MJ&cauthor_id=26433354) [2](https://pubmed.ncbi.nlm.nih.gov/26433354-identifying-genetic-determinants-of-autoimmunity-and-immune-dysregulation/?from_single_result=lucas+cl+determinants+of+autoimmunity+review#affiliation-2)

## Abstract

Common autoimmune diseases are relatively heterogeneous with both genetic and environmental factors influencing disease susceptibility and progression. As the populations in developed countries age, these chronic diseases will become an increasing burden in human suffering and health care costs. By contrast, rare immune diseases that are severe and develop early in childhood are frequently monogenic and fully penetrant, often with a Mendelian inheritance pattern. Although these may be incompatible with survival or cured by hematopoietic stem cell transplantation, we will argue that they constitute a rich source of genetic insights into immunological diseases. Here, we discuss five examples of well-studied Mendelian disease-causing genes and their known or predicted roles in conferring susceptibility to common, polygenic diseases of autoimmunity. Mendelian disease mutations, as experiments of nature, reveal human loci that are indispensable for immune regulation and, therefore, most promising as therapeutic targets.

[Cell.](http://www.ncbi.nlm.nih.gov/pubmed/?term=Zenewicz+LA+Unraveling+the+genetics+of+autoimmunity) 2010 Mar 19;140(6):791-7. doi: 10.1016/j.cell.2010.03.003.

**Unraveling the genetics of autoimmunity.**

[Zenewicz LA](http://www.ncbi.nlm.nih.gov/pubmed?term=Zenewicz%20LA%5BAuthor%5D&cauthor=true&cauthor_uid=20303870), [Abraham C](http://www.ncbi.nlm.nih.gov/pubmed?term=Abraham%20C%5BAuthor%5D&cauthor=true&cauthor_uid=20303870), [Flavell RA](http://www.ncbi.nlm.nih.gov/pubmed?term=Flavell%20RA%5BAuthor%5D&cauthor=true&cauthor_uid=20303870), [Cho JH](http://www.ncbi.nlm.nih.gov/pubmed?term=Cho%20JH%5BAuthor%5D&cauthor=true&cauthor_uid=20303870).

**Abstract**

The chronic autoimmune diseases include multiple complex genetic disorders. Recently, genome-wide association studies (GWAS) have identified a large number of major loci, with many associations shared between various autoimmune diseases. These associations highlight key roles for lymphocyte activation and prioritize specific cytokine pathways and mechanisms of host-microbe recognition. Despite success in identifying loci, comprehensive models of disease pathogenesis are currently lacking. Future efforts comparing association patterns between autoimmune diseases may be particularly illustrative. New genomic technologies applied to classic genetic studies involving twins, early onset cases, and phenotypic extremes may provide key insights into developmental and gene-environment interactions in autoimmunity.

[Nat Rev Rheumatol.](https://www.ncbi.nlm.nih.gov/pubmed/?term=stanford+sm+bottini+n+ptpn22+review+2014) 2014 Oct;10(10):602-11. doi: 10.1038/nrrheum.2014.109. Epub 2014 Jul 8.

# PTPN22: the archetypal non-HLA autoimmunity gene.

[Stanford SM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Stanford%20SM%5BAuthor%5D&cauthor=true&cauthor_uid=25003765)1, [Bottini N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bottini%20N%5BAuthor%5D&cauthor=true&cauthor_uid=25003765)1.

### Abstract

PTPN22 encodes a tyrosine phosphatase that is expressed by haematopoietic cells and functions as a key regulator of immune homeostasis by inhibiting T-cell receptor signalling and by selectively promoting type I interferon responses after activation of myeloid-cell pattern-recognition receptors. A single nucleotide polymorphism of PTPN22, 1858C>T (rs2476601), disrupts an interaction motif in the protein, and is the most important non-HLA genetic risk factor for rheumatoid arthritis and the second most important for juvenile idiopathic arthritis. PTPN22 exemplifies a shared autoimmunity gene, affecting the pathogenesis of systemic lupus erythematosus, vasculitis and other autoimmune diseases. In this Review, we explore the role of PTPN22 in autoimmune connective tissue disease, with particular emphasis on candidate-gene and genome-wide association studies and clinical variability of disease. We also propose a number of PTPN22-dependent functional models of the pathogenesis of autoimmune diseases.

[Curr Opin Immunol.](https://www.ncbi.nlm.nih.gov/pubmed/29128729) 2017 Nov 9;50:32-38. doi: 10.1016/j.coi.2017.10.011.

# Recent advances in inflammasome biology.

[Place DE](https://www.ncbi.nlm.nih.gov/pubmed/?term=Place%20DE%5BAuthor%5D&cauthor=true&cauthor_uid=29128729), [Kanneganti TD](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kanneganti%20TD%5BAuthor%5D&cauthor=true&cauthor_uid=29128729).

### Abstract

The inflammasome is a complex of proteins that through the activity of caspase-1 and the downstream substrates gasdermin D, IL-1β, and IL-18 execute an inflammatory form of cell death termed pyroptosis. Activation of this complex often involves the adaptor protein ASC and upstream sensors including NLRP1, NLRP3, NLRC4, AIM2, and pyrin, which are activated by different stimuli including infectious agents and changes in cell homeostasis. Here we discuss new regulatory mechanisms that have been identified for the canonical inflammasomes, the most recently identified NLRP9b inflammasome, and the new gasdermin family of proteins that mediate pyroptosis and other forms of regulated cell death.

[Trends Immunol.](http://www.ncbi.nlm.nih.gov/pubmed/?term=Wing+K+Cell+autonomous+and+non-autonomous++role+of+CTLA4) 2011 Sep;32(9):428-33. doi: 10.1016/j.it.2011.06.002. Epub 2011 Jun 30.

# Cell-autonomous and -non-autonomous roles of

# CTLA-4 in immune regulation.

[Wing K](http://www.ncbi.nlm.nih.gov/pubmed?term=Wing%20K%5BAuthor%5D&cauthor=true&cauthor_uid=21723783), [Yamaguchi T](http://www.ncbi.nlm.nih.gov/pubmed?term=Yamaguchi%20T%5BAuthor%5D&cauthor=true&cauthor_uid=21723783), [Sakaguchi S](http://www.ncbi.nlm.nih.gov/pubmed?term=Sakaguchi%20S%5BAuthor%5D&cauthor=true&cauthor_uid=21723783).

### Abstract

It is controversial how cytotoxic T lymphocyte antigen (CTLA)-4, a co-inhibitory molecule, contributes to immunological tolerance and negative control of immune responses. Its role as an inducer of cell-intrinsic negative signals to activated effector T cells is well documented. However, there is accumulating evidence that CTLA-4 is essential for the function of naturally occurring Foxp3(+) regulatory T (Treg) cells, which constitutively express the molecule. CTLA-4 deficiency in Foxp3(+) Treg cells indeed impairs their in vivo and in vitro suppressive function. Further, Treg cells can modulate the function of CD80- and CD86-expressing antigen-presenting cells via CTLA-4. Here we discuss how CTLA-4 expression by one T cell can influence the activation of another in a cell non-autonomous fashion and thus control immune responses.

[Sci Signal.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Vang+a+swicth+variant+model+integrates+2018+review) 2018 Apr 17;11(526). pii: eaat0936. doi: 10.1126/scisignal.aat0936.

**A switch-variant model integrates the functions of an autoimmune variant of the phosphatase PTPN22.**

[Vang T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Vang%20T%5BAuthor%5D&cauthor=true&cauthor_uid=29666305), [Nielsen J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Nielsen%20J%5BAuthor%5D&cauthor=true&cauthor_uid=29666305), [Burn GL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Burn%20GL%5BAuthor%5D&cauthor=true&cauthor_uid=29666305)

### Abstract

The R620W polymorphism in protein tyrosine phosphatase nonreceptor type 22 (PTPN22) predisposes carriers to several autoimmune diseases. Two papers in *Science Immunology* and *Science Signaling* on this human disease-associated variant lead us to propose a new "switch-of-function" model.

[Nat Rev Immunol.](https://www.ncbi.nlm.nih.gov/pubmed/?term=central+tolerance+Nemazee+D+2017+review) 2017 May;17(5):281-294. doi: 10.1038/nri.2017.19. Epub 2017 Apr 3.

# Mechanisms of central tolerance for B cells.

[Nemazee D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Nemazee%20D%5BAuthor%5D&cauthor=true&cauthor_uid=28368006).

### Abstract

Immune tolerance hinders the potentially destructive responses of lymphocytes to host tissues. Tolerance is regulated at the stage of immature B cell development (central tolerance) by clonal deletion, involving apoptosis, and by receptor editing, which reprogrammes the specificity of B cells through secondary recombination of antibody genes. Recent mechanistic studies have begun to elucidate how these divergent mechanisms are controlled. Single-cell antibody cloning has revealed defects of B cell central tolerance in human autoimmune diseases and in several human immunodeficiency diseases caused by single gene mutations, which indicates the relevance of B cell tolerance to disease and suggests possible genetic pathways that regulate tolerance.

[Nat Immunol.](https://www.ncbi.nlm.nih.gov/pubmed/?term=von+Boehmer+H+Checkpoints+in+lymphocyte+development+and+autoimmune) 2010 Jan;11(1):14-20. doi: 10.1038/ni.1794. Epub 2009 Dec 17.

# Checkpoints in lymphocyte development

# and autoimmune disease.

[von Boehmer H](https://www.ncbi.nlm.nih.gov/pubmed/?term=von%20Boehmer%20H%5BAuthor%5D&cauthor=true&cauthor_uid=20016505)1, [Melchers F](https://www.ncbi.nlm.nih.gov/pubmed/?term=Melchers%20F%5BAuthor%5D&cauthor=true&cauthor_uid=20016505).

### Abstract

Antigen receptor-controlled checkpoints in B lymphocyte development are crucial for the prevention of autoimmune diseases such as systemic lupus erythematosus. Checkpoints at the stage of pre-B cell receptor (pre-BCR) and BCR expression can eliminate certain autoreactive BCRs either by deletion of or anergy induction in cells expressing autoreactive BCRs or by receptor editing. For T cells, the picture is more complex because there are regulatory T (T(reg)) cells that mediate dominant tolerance, which differs from the recessive tolerance mediated by deletion and anergy. Negative selection of thymocytes may be as essential as T(reg) cell generation in preventing autoimmune diseases such as type 1 diabetes, but supporting evidence is scarce. Here we discuss several scenarios in which failures at developmental checkpoints result in autoimmunity.

[Nat Rev Immunol.](http://www.ncbi.nlm.nih.gov/pubmed/?term=Takahama+Y.+Journey+through+the+thymus) 2006 Feb;6(2):127-35.

**Journey through the thymus: stromal guides for T-cell development and selection.**

[Takahama Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Takahama%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=16491137).

**Abstract**

Lympho-stromal interactions in multiple microenvironments within the thymus have a crucial role in the regulation of T-cell development and selection. Recent studies have implicated that chemokines that are produced by thymic stromal cells have a pivotal role in positioning developing T cells within the thymus. In this Review, I discuss the importance of stroma-derived chemokines in guiding the traffic of developing thymocytes, with an emphasis on the processes of cortex-to-medulla migration and T-cell-repertoire selection, including central tolerance.

[Nat Rev Immunol.](http://www.ncbi.nlm.nih.gov/pubmed/24830344) 2014 Jun;14(6):377-91. doi: 10.1038/nri3667. Epub 2014 May 16.

# Positive and negative selection of the T cell repertoire:

# what thymocytes see (and don't see).

[Klein L](http://www.ncbi.nlm.nih.gov/pubmed/?term=Klein%20L%5BAuthor%5D&cauthor=true&cauthor_uid=24830344)1, [Kyewski B](http://www.ncbi.nlm.nih.gov/pubmed/?term=Kyewski%20B%5BAuthor%5D&cauthor=true&cauthor_uid=24830344)2, [Allen PM](http://www.ncbi.nlm.nih.gov/pubmed/?term=Allen%20PM%5BAuthor%5D&cauthor=true&cauthor_uid=24830344)3, [Hogquist KA](http://www.ncbi.nlm.nih.gov/pubmed/?term=Hogquist%20KA%5BAuthor%5D&cauthor=true&cauthor_uid=24830344)4.

### Abstract

The fate of developing T cells is specified by the interaction of their antigen receptors with self-peptide-MHC complexes that are displayed by thymic antigen-presenting cells (APCs). Various subsets of thymic APCs are strategically positioned in particular thymic microenvironments and they coordinate the selection of a functional and self-tolerant T cell repertoire. In this Review, we discuss the different strategies that these APCs use to sample and process self antigens and to thereby generate partly unique, 'idiosyncratic' peptide-MHC ligandomes. We discuss how the particular composition of the peptide-MHC ligandomes that are presented by specific APC subsets not only shapes the T cell repertoire in the thymus but may also indelibly imprint the behaviour of mature T cells in the periphery.

[Curr Opin Immunol.](http://www.ncbi.nlm.nih.gov/pubmed/?term=Takahama+Y.++%CE%B25t-containing+thymoproteasome%3A+specific+expression) 2012 Feb;24(1):92-8. doi: 10.1016/j.coi.2012.01.006. Epub 2012 Jan 27.

# β5t-containing thymoproteasome: specific expression in thymic cortical epithelial cells and role in positive selection of CD8+ T cells.

[Takahama Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Takahama%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=22285892), [Takada K](http://www.ncbi.nlm.nih.gov/pubmed?term=Takada%20K%5BAuthor%5D&cauthor=true&cauthor_uid=22285892), [Murata S](http://www.ncbi.nlm.nih.gov/pubmed?term=Murata%20S%5BAuthor%5D&cauthor=true&cauthor_uid=22285892), [Tanaka K](http://www.ncbi.nlm.nih.gov/pubmed?term=Tanaka%20K%5BAuthor%5D&cauthor=true&cauthor_uid=22285892).

### Abstract

Proteasomes are multisubunit proteolytic complexes that degrade cytoplasmic and nuclear proteins in eukaryotes. Proteasome-dependent proteolysis contributes to various cellular processes, including misfolded protein degradation, signal transduction, and antigen presentation. The thymoproteasome is a form of proteasome that contains the vertebrate-specific catalytic subunit β5t specifically expressed by cortical epithelial cells in the thymus. The thymoproteasome is essential for the positive selection of CD8+ T cells that carry an immunocompetent repertoire of antigen recognition specificity. Here we summarize the structure and expression of the thymoproteasome and discuss how it regulates the positive selection of CD8+ T cells.

[Eur J Immunol.](http://www.ncbi.nlm.nih.gov/pubmed/26450177) 2016 Jan;46(1):22-33. doi: 10.1002/eji.201545792. Epub 2015 Nov 2.

# AIRE: From promiscuous molecular partnerships

# to promiscuous gene expression.

[Abramson J](http://www.ncbi.nlm.nih.gov/pubmed/?term=Abramson%20J%5BAuthor%5D&cauthor=true&cauthor_uid=26450177)1, [Goldfarb Y](http://www.ncbi.nlm.nih.gov/pubmed/?term=Goldfarb%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=26450177)1.

### Abstract

Autoimmune regulator (AIRE) is a unique transcriptional regulator that induces promiscuous expression of thousands of tissue-restricted antigens (TRAs) in medullary thymic epithelial cells (mTECs), a step critical for the induction of immunological self-tolerance. The past 15 years have seen dramatic progress in our understanding of how AIRE induces immunological self-tolerance on a molecular level. This major advancement can be greatly attributed to the identification of a large variety of proteins that physically associate with AIRE, supporting and regulating its transcription-transactivation capacity. These diverse molecular partnerships have been shown to play roles in shuttling AIRE to the nucleus, securing AIRE's interaction with nuclear matrix and chromatin, releasing RNA polymerase-II from its stalled state and potentiating AIRE-mediated gene expression, among others. In this review we discuss the relationship of AIRE with its vast and rather diverse repertoire of partners and highlight how such "promiscuous partnerships" contribute to the phenomenon of "promiscuous gene expression" in the thymus.

[Nat Rev Immunol.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Anderson+MS++AIRE+expands%3A+new+roles+in+immune+tolerance+and+beyond) 2016 Apr;16(4):247-58. doi: 10.1038/nri.2016.9. Epub 2016 Mar 14.

# AIRE expands: new roles in immune tolerance and beyond.

[Anderson MS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Anderson%20MS%5BAuthor%5D&cauthor=true&cauthor_uid=26972725), [Su MA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Su%20MA%5BAuthor%5D&cauthor=true&cauthor_uid=26972725)

### Abstract

More than 15 years ago, mutations in the autoimmune regulator (AIRE) gene were identified as the cause of autoimmune polyglandular syndrome type 1 (APS1). It is now clear that this transcription factor has a crucial role in promoting self-tolerance in the thymus by regulating the expression of a wide array of self-antigens that have the commonality of being tissue-restricted in their expression pattern in the periphery. In this Review, we highlight many of the recent advances in our understanding of the complex biology that is related to AIRE, with a particular focus on advances in genetics, molecular interactions and the effect of AIRE on thymic selection of regulatory T cells. Furthermore, we highlight new areas of biology that are potentially affected by this key regulator of immune tolerance.

[Ann N Y Acad Sci.](https://www.ncbi.nlm.nih.gov/pubmed/?term=aire%3A+a+missing+link+to+explain+2018+review) 2018 Jan;1412(1):21-32. doi: 10.1111/nyas.13529.

# AIRE: a missing link to explain female susceptibility to

# autoimmune diseases.

[Berrih-Aknin S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Berrih-Aknin%20S%5BAuthor%5D&cauthor=true&cauthor_uid=29291257), [Panse RL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Panse%20RL%5BAuthor%5D&cauthor=true&cauthor_uid=29291257), [Dragin N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Dragin%20N%5BAuthor%5D&cauthor=true&cauthor_uid=29291257)

### Abstract

Women are more susceptible to autoimmune diseases than men. Autoimmunity results from tolerance breakdown toward self-components. Recently, three transcription modulators were identified in medullary thymic epithelial cells that orchestrate immune central tolerance processes: the autoimmune regulator (AIRE), FEZ family zinc finger 2 (FEZF2 or FEZ1), and PR domain zinc finger protein 1 (PRDM1). Interestingly, these three transcription modulators regulate nonredundant tissue-specific antigen subsets and thus cover broad antigen diversity. Recent data from different groups demonstrated that sex hormones (estrogen and testosterone) are involved in the regulation of thymic AIRE expression in humans and mice through direct transcriptional modulation and epigenetic changes. As a consequence, AIRE displays gender-biased thymic expression, with females showing a lower expression compared with males, a finding that could explain the female susceptibility to autoimmune diseases. So far, FEZF2 has not been related to an increased gender bias in autoimmune disease. PRDM1 expression has not been shown to display gender-differential thymic expression, but its expression level and its gene polymorphisms are associated with female-dependent autoimmune disease risk. Altogether, various studies have demonstrated that increased female susceptibility to autoimmune diseases is in part a consequence of hormone-driven reduced thymic AIRE expression.

[Trends Immunol.](https://www.ncbi.nlm.nih.gov/pubmed/?term=takaba+h+takayanagi+h+t+cell+selection+review) 2017 Nov;38(11):805-816. doi: 10.1016/j.it.2017.07.010. Epub 2017 Aug 19.

# The Mechanisms of T Cell Selection in the Thymus.

[Takaba H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Takaba%20H%5BAuthor%5D&cauthor=true&cauthor_uid=28830733)1, [Takayanagi H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Takayanagi%20H%5BAuthor%5D&cauthor=true&cauthor_uid=28830733)2.

### Abstract

T cells undergo positive and negative selection in the thymic cortex and medulla, respectively. A promiscuous expression of a wide array of self-antigens in the thymus is essential for the negative selection of self-reactive T cells and the establishment of central tolerance. Aire was originally thought to be the exclusive factor regulating the expression of tissue-restricted antigens, but Fezf2 recently emerged as a critical transcription factor in this regulatory activity. Fezf2 is selectively expressed in thymic medullary epithelial cells, regulates a large number of tissue-restricted antigens and suppresses the onset of autoimmune responses. Here, we discuss novel findings on the transcriptional mechanisms of tissue restricted-antigen expression in the medullary thymic epithelial cells and its effects on T cell selection.

J Immunol 203 (8), 2031-2041 2019 Oct 15

#  Regulatory T Cell Development in the Thymus

[David L Owen](https://pubmed.ncbi.nlm.nih.gov/?term=Owen+DL&cauthor_id=31591259) [1](https://pubmed.ncbi.nlm.nih.gov/31591259-regulatory-t-cell-development-in-the-thymus/?from_term=Owen+dl+regulatory+t+cell+review&from_pos=1#affiliation-1) , [Louisa E Sjaastad](https://pubmed.ncbi.nlm.nih.gov/?term=Sjaastad+LE&cauthor_id=31591259) [1](https://pubmed.ncbi.nlm.nih.gov/31591259-regulatory-t-cell-development-in-the-thymus/?from_term=Owen+dl+regulatory+t+cell+review&from_pos=1#affiliation-1) , [Michael A Farrar](https://pubmed.ncbi.nlm.nih.gov/?term=Farrar+MA&cauthor_id=31591259) [1](https://pubmed.ncbi.nlm.nih.gov/31591259-regulatory-t-cell-development-in-the-thymus/?from_term=Owen+dl+regulatory+t+cell+review&from_pos=1#affiliation-1)

## Abstract

Development of a comprehensive regulatory T (Treg) cell compartment in the thymus is required to maintain immune homeostasis and prevent autoimmunity. In this study, we review cellular and molecular determinants of Treg cell development in the thymus. We focus on the evidence for a self-antigen-focused Treg cell repertoire as well as the APCs responsible for presenting self-antigens to developing thymocytes. We also cover the contribution of different cytokines to thymic Treg development and the cellular populations that produce these cytokines. Finally, we update the originally proposed "two-step" model of thymic Treg differentiation by incorporating new evidence demonstrating that Treg cells develop from two Treg progenitor populations and discuss the functional importance of Treg cells generated via either progenitor pathway.

Frontiers in Immunology 2021 Apr 2;12:635569.

# Post-Aire Medullary Thymic Epithelial Cells and Hassall's Corpuscles as Inducers of Tonic Pro-Inflammatory Microenvironment

[Martti Laan](https://pubmed.ncbi.nlm.nih.gov/?sort=date&size=100&term=Laan+M&cauthor_id=33868260) [1](https://pubmed.ncbi.nlm.nih.gov/33868260/#affiliation-1) , [Ahto Salumets](https://pubmed.ncbi.nlm.nih.gov/?sort=date&size=100&term=Salumets+A&cauthor_id=33868260) [1](https://pubmed.ncbi.nlm.nih.gov/33868260/#affiliation-1)  [2](https://pubmed.ncbi.nlm.nih.gov/33868260/#affiliation-2) , [Annabel Klein](https://pubmed.ncbi.nlm.nih.gov/?sort=date&size=100&term=Klein+A&cauthor_id=33868260) [1](https://pubmed.ncbi.nlm.nih.gov/33868260/#affiliation-1) , [Kerli Reintamm](https://pubmed.ncbi.nlm.nih.gov/?sort=date&size=100&term=Reintamm+K&cauthor_id=33868260) [1](https://pubmed.ncbi.nlm.nih.gov/33868260/#affiliation-1) , [Rudolf Bichele](https://pubmed.ncbi.nlm.nih.gov/?sort=date&size=100&term=Bichele+R&cauthor_id=33868260) [1](https://pubmed.ncbi.nlm.nih.gov/33868260/#affiliation-1) , [Hedi Peterson](https://pubmed.ncbi.nlm.nih.gov/?sort=date&size=100&term=Peterson+H&cauthor_id=33868260) [2](https://pubmed.ncbi.nlm.nih.gov/33868260/#affiliation-2) , [Pärt Peterson](https://pubmed.ncbi.nlm.nih.gov/?sort=date&size=100&term=Peterson+P&cauthor_id=33868260) [1](https://pubmed.ncbi.nlm.nih.gov/33868260/#affiliation-1)

Abstract

While there is convincing evidence on the role of Aire-positive medullary thymic epithelial cells (mTEC) in the induction of central tolerance, the nature and function of post-Aire mTECs and Hassall's corpuscles have remained enigmatic. Here we summarize the existing data on these late stages of mTEC differentiation with special focus on their potential to contribute to central tolerance induction by triggering the unique pro-inflammatory microenvironment in the thymus. In order to complement the existing evidence that has been obtained from mouse models, we performed proteomic analysis on microdissected samples from human thymic medullary areas at different differentiation stages. The analysis confirms that at the post-Aire stages, the mTECs lose their nuclei but maintain machinery required for translation and exocytosis and also upregulate proteins specific to keratinocyte differentiation and cornification. In addition, at the late stages of differentiation, the human mTECs display a distinct pro-inflammatory signature, including upregulation of the potent endogenous TLR4 agonist S100A8/S100A9. Collectively, the study suggests a novel mechanism by which the post-Aire mTECs and Hassall's corpuscles contribute to the thymic microenvironment with potential cues on the induction of central tolerance.

 [Cell.](http://www.ncbi.nlm.nih.gov/pubmed/18510923) 2008 May 30;133(5):775-87. doi: 10.1016/j.cell.2008.05.009.

**Regulatory T cells and immune tolerance.**

[Sakaguchi S](http://www.ncbi.nlm.nih.gov/pubmed?term=Sakaguchi%20S%5BAuthor%5D&cauthor=true&cauthor_uid=18510923), [Yamaguchi T](http://www.ncbi.nlm.nih.gov/pubmed?term=Yamaguchi%20T%5BAuthor%5D&cauthor=true&cauthor_uid=18510923), [Nomura T](http://www.ncbi.nlm.nih.gov/pubmed?term=Nomura%20T%5BAuthor%5D&cauthor=true&cauthor_uid=18510923), [Ono M](http://www.ncbi.nlm.nih.gov/pubmed?term=Ono%20M%5BAuthor%5D&cauthor=true&cauthor_uid=18510923).

**Abstract**

Regulatory T cells (Tregs) play an indispensable role in maintaining immunological unresponsiveness to self-antigens and in suppressing excessive immune responses deleterious to the host. Tregs are produced in the thymus as a functionally mature subpopulation of T cells and can also be induced from naive T cells in the periphery. Recent research reveals the cellular and molecular basis of Treg development and function and implicates dysregulation of Tregs in immunological disease.

[Curr Opin Immunol.](http://www.ncbi.nlm.nih.gov/pubmed/?term=doyle+ha+autoantigenesis) 2012 Feb;24(1):112-8. doi: 10.1016/j.coi.2011.12.003. Epub 2011 Dec 29.

# Autoantigenesis: the evolution of protein modifications

# in autoimmune disease.

[Doyle HA](http://www.ncbi.nlm.nih.gov/pubmed/?term=Doyle%20HA%5BAuthor%5D&cauthor=true&cauthor_uid=22209691)1, [Mamula MJ](http://www.ncbi.nlm.nih.gov/pubmed/?term=Mamula%20MJ%5BAuthor%5D&cauthor=true&cauthor_uid=22209691).

### Abstract

Protein targets in autoimmune disease vary in location, originating within cells as in system lupus erythematosus (SLE), or found on cell surfaces or in extracellular spaces. The term 'autoantigenesis' is first defined here as the changes that arise in self-proteins as they break self-tolerance and trigger autoimmune B and/or T cell responses. As illustrated in many studies, between 50 and 90% of the proteins in the human body acquire post-translational modification. In some cases, it may be that these modifications are necessary for the biological functions of proteins of the cells in which they reside or as extracellular mediators. Summarized herein, it is clear that some post-translational modifications can create new self-antigens by altering immunologic processing and presentation. While many protein modifications exist, we will focus on those created, amplified, or altered in the context of inflammation or other immune system responses. Finally, we will address how post-translational modifications in self-antigens may affect the analyses of B and T cell specificity, current diagnostic techniques, and/or the development of immunotherapies for autoimmune diseases.

[Curr Opin Immunol.](http://www.ncbi.nlm.nih.gov/pubmed/21917438) 2011 Dec;23(6):732-8. doi: 10.1016/j.coi.2011.08.006. Epub 2011 Sep 12.

**Celiac disease and transglutaminase 2: a model for posttranslational modification of antigens and HLA association in the pathogenesis of autoimmune disorders.**

[Sollid LM](http://www.ncbi.nlm.nih.gov/pubmed?term=Sollid%20LM%5BAuthor%5D&cauthor=true&cauthor_uid=21917438), [Jabri B](http://www.ncbi.nlm.nih.gov/pubmed?term=Jabri%20B%5BAuthor%5D&cauthor=true&cauthor_uid=21917438).

**Abstract**

Posttranslational modification (PTM) of antigen is a way to break T-cell tolerance to self-antigens and promote autoimmunity. However, the precise mechanisms by which modifications would facilitate autoimmune T-cell responses and how they relate to particular autoimmune-associated MHC molecules remain elusive. Celiac disease is a T-cell mediated enteropathy with a strong HLA association where the immune response is directed mainly against deamidated cereal gluten peptides that have been modified by the enzyme transglutaminase 2. The disease is further characterized by autoantibodies to transglutaminase 2 that have extraordinary high disease specificity and sensitivity. There have been important advances in the knowledge of celiac disease pathogenesis, and these insights may be applicable to other autoimmune disorders where PTM plays a role. This insight gives clues for understanding the involvement of PTMs in other autoimmune diseases.

Curr Opin Immunol 2019 Dec;61:69-73. doi: 10.1016/j.coi.2019.08.005.

#  On the mark: genetically engineered immunotherapies for autoimmunity

[Christoph T Ellebrecht](https://pubmed.ncbi.nlm.nih.gov/?sort=date&size=200&term=Ellebrecht+CT&cauthor_id=31563849) [1](https://pubmed.ncbi.nlm.nih.gov/31563849/#affiliation-1) , [Daniel K Lundgren](https://pubmed.ncbi.nlm.nih.gov/?sort=date&size=200&term=Lundgren+DK&cauthor_id=31563849) [1](https://pubmed.ncbi.nlm.nih.gov/31563849/#affiliation-1) , [Aimee S Payne](https://pubmed.ncbi.nlm.nih.gov/?sort=date&size=200&term=Payne+AS&cauthor_id=31563849) [2](https://pubmed.ncbi.nlm.nih.gov/31563849/#affiliation-2)

Affiliations DOI: [10.1016/j.coi.2019.08.005](https://doi.org/10.1016/j.coi.2019.08.005)

## Abstract

Current therapies for autoimmunity cause significant morbidity and mortality. Adoptive immunotherapy using genetically engineered T cells has led to durable remissions of B cell leukemias and lymphomas, raising the question of whether the approach can be modified to target autoreactive B and T cells to induce durable remissions of autoimmunity. Here we review antigen-specific approaches to modify immune cells to treat autoimmune disease. We focus on recent studies that aim to eliminate or suppress autoimmunity by targeting the disease-causing B or T cells through their B cell receptor or T cell receptor specificities.