

Central Tolerance

Immature lymphocyte selection and protection from autoimmunity

T-cell selection in thymus

B-cell selection in marrow

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

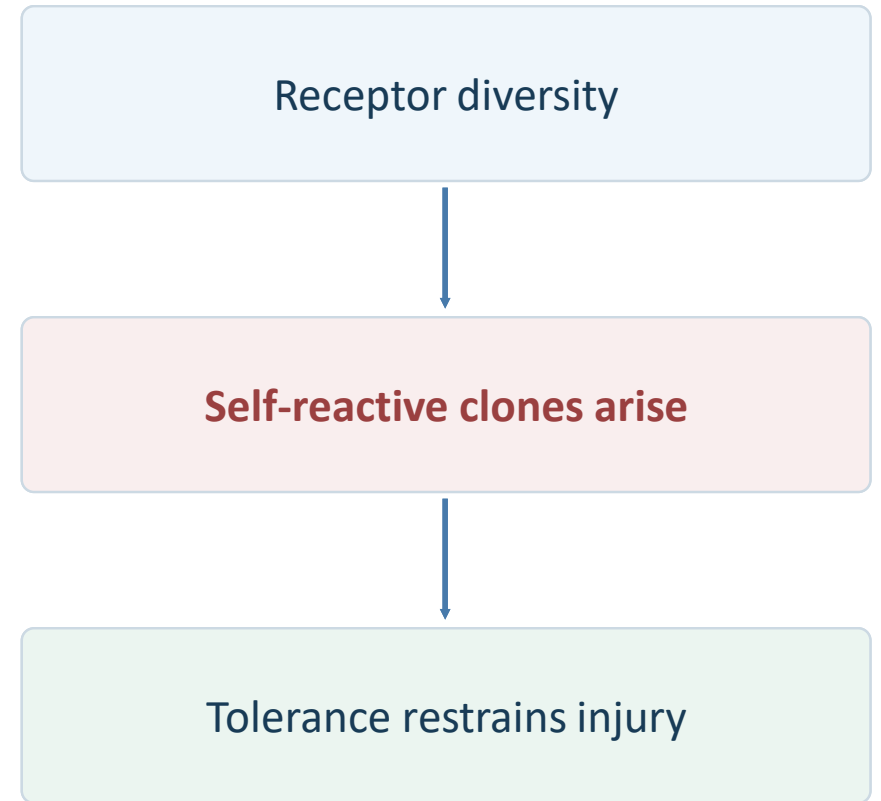
Interpret central tolerance as a linked series of developmental checkpoints.

- Explain why somatic receptor rearrangement creates self-reactive clones.
- Trace thymic deletion, AIRE-dependent self-antigen display and thymic Treg development.
- Explain bone-marrow receptor editing versus apoptotic B-cell deletion.
- Connect imperfect central selection to peripheral tolerance and autoimmunity.

Self-tolerance prevents immune injury

Autoreactivity must be controlled before it becomes pathogenic.

- Antigen receptors are diverse enough to recognize many molecular structures.
- Some newly generated receptors recognize components of the host.
- Tolerance prevents these potential responses from damaging normal tissue.



Immunologic tolerance is antigen-specific unresponsiveness

Exposure to an antigen can establish a state of unresponsiveness.

- Immunologic tolerance describes unresponsiveness induced by antigen exposure.
- Self-tolerance refers specifically to an individual's own antigens.
- The distinction is the identity of the antigen, not a separate immune system.

Immunologic tolerance

Unresponsiveness to an antigen

Self-tolerance

Unresponsiveness to self antigens

Central tolerance acts during lymphocyte maturation

Immature clones are tested in primary lymphoid organs.

- Developing lymphocytes are assessed before joining the mature repertoire.
- The thymus is the central tolerance site for T lymphocytes.
- Bone marrow is the corresponding site for B lymphocytes.

Thymus

Developing T cells

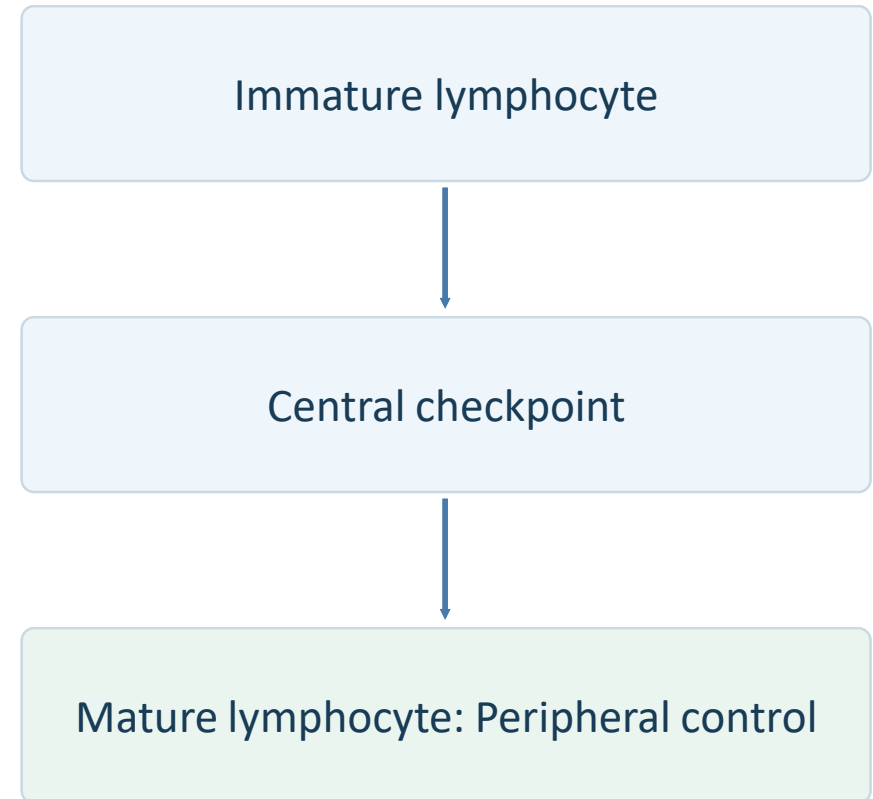
Bone marrow

Developing B cells

Central and peripheral tolerance are complementary

Tolerance has a developmental checkpoint and a later safety net.

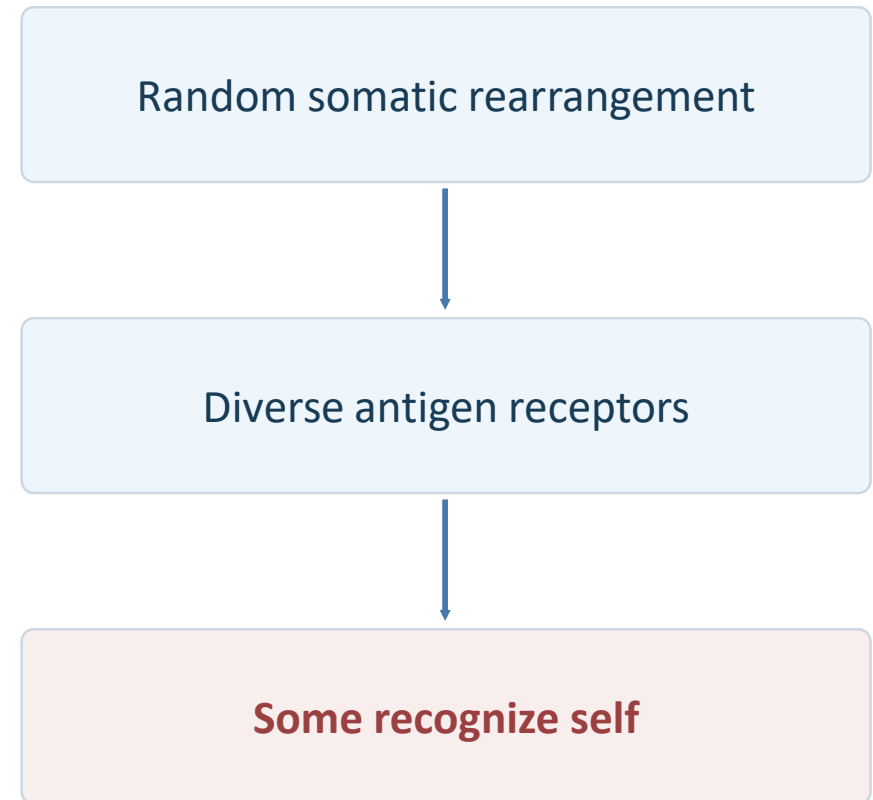
- Central mechanisms operate during maturation in generative organs.
- Peripheral mechanisms restrain mature self-reactive cells after their exit.
- The second tier is necessary because central selection is not complete.



Random receptor rearrangement creates the problem

Antigen-receptor diversity is generated without foreknowledge of self.

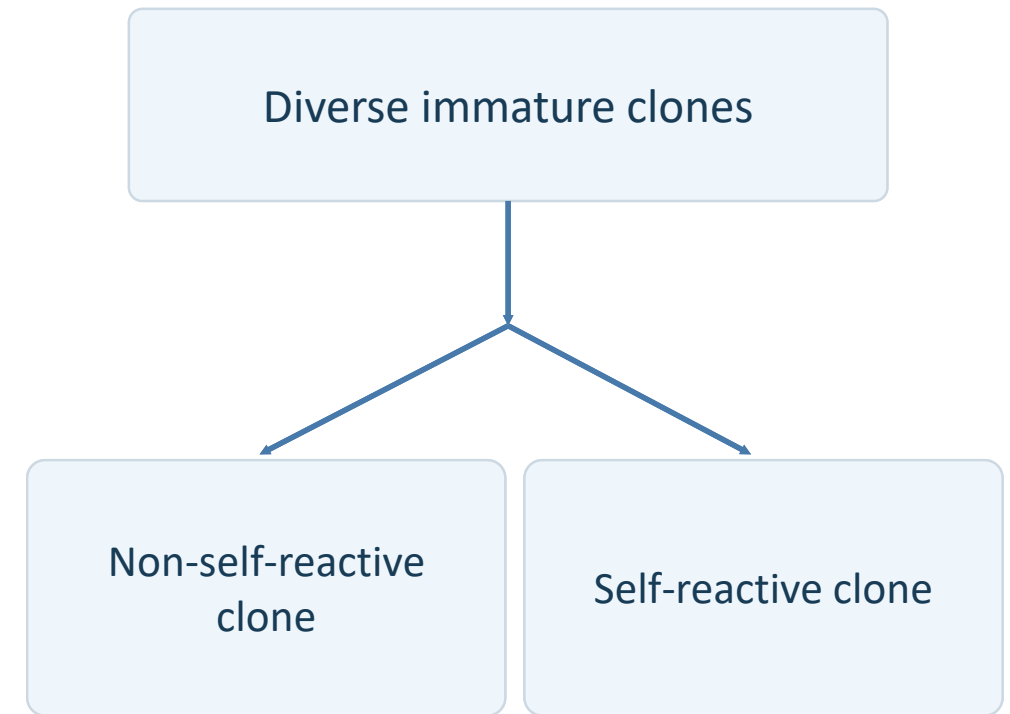
- Somatic gene rearrangements generate distinct antigen receptors.
- A subset of receptors acquires high affinity for self antigens by chance.
- Tolerance is therefore an essential consequence of normal receptor diversity.



Self-reactivity is initially a property of the receptor

Selection addresses specific developing clones—not all lymphocytes.

- The relevant signal depends on recognition by a particular receptor.
- Different developing clones can react to different self antigens.
- Eliminating or changing a dangerous clone preserves the broader repertoire.

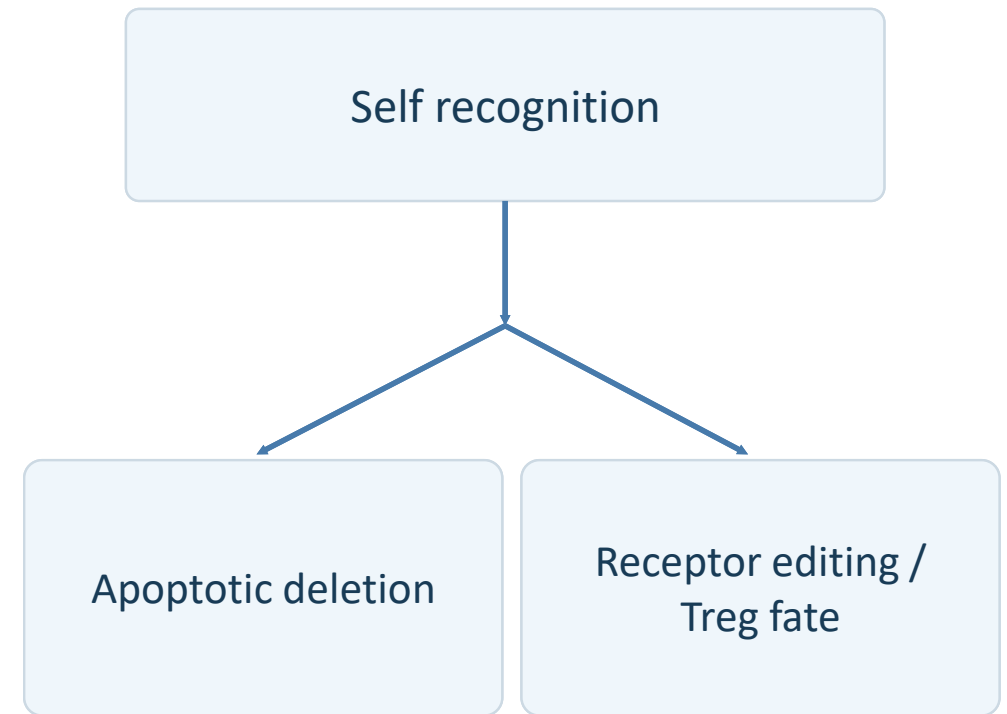


Alternative outcomes

Central tolerance makes cells harmless by different routes

Deletion is not the only possible central outcome.

- Self-reactive cells may be removed through apoptosis.
- Developing B cells may change receptor specificity by receptor editing.
- Some CD4-lineage T cells recognizing self differentiate into regulatory T cells.



Alternative outcomes

A conceptual map of the two central organs

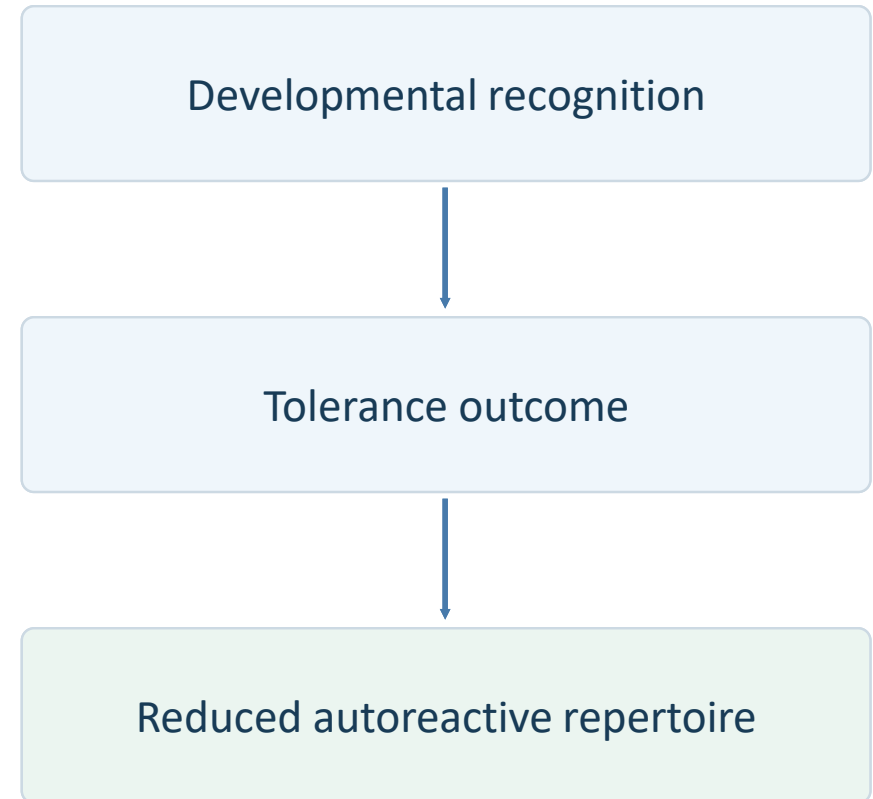
The organ and lineage determine the dominant tolerance options.

Feature	T-cell pathway	B-cell pathway
Central site	Thymus	Bone marrow
Principal mechanism	Clonal deletion	Receptor editing / deletion
Additional fate	Thymic Treg generation	No analogous fate described here

Central selection is preventive, not a clinical diagnosis

Central tolerance is a developmental mechanism.

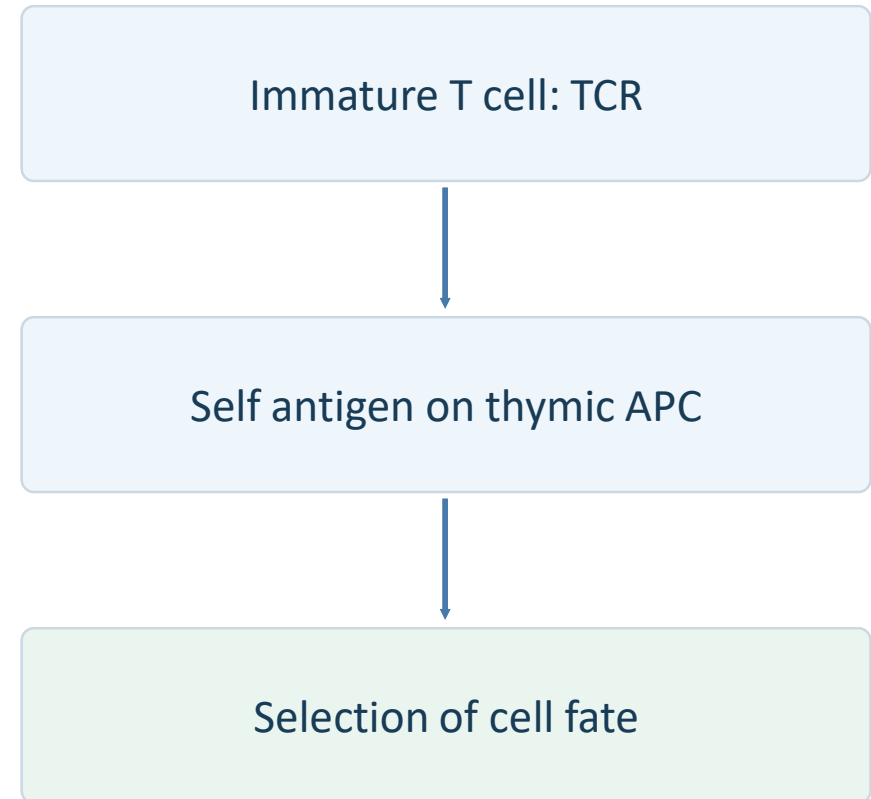
- The normal process does not require tissue inflammation or visible pathology.
- Clinical disease appears when failures permit harmful autoimmune responses.
- Its mechanisms are best taught through receptor–antigen interactions.



The thymus is the T-cell selection environment

Developing T lymphocytes encounter self antigens within the thymus.

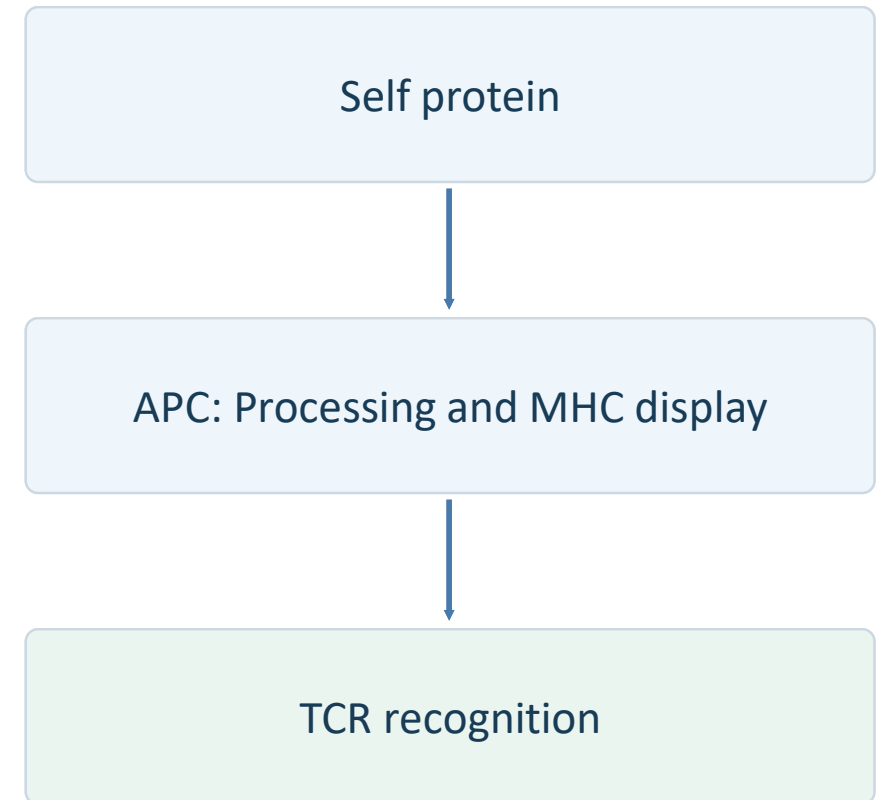
- Immature T cells express newly generated T-cell receptors (TCRs).
- Autologous antigens are processed and presented by thymic antigen-presenting cells.
- Recognition can trigger deletion or, in a subset, a regulatory lineage.



TCR recognition is directed at antigen on self MHC

Presentation determines which self determinants can be seen.

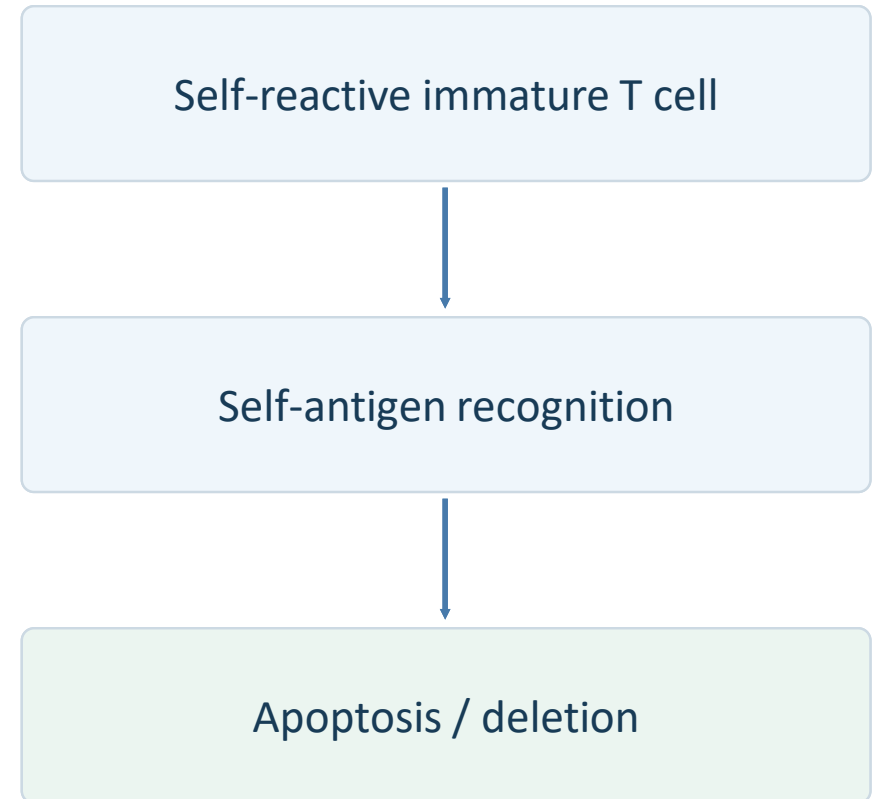
- Thymic antigen-presenting cells display processed protein antigens.
- These are presented in association with self MHC molecules.
- An immature TCR can therefore encounter host-derived peptide–MHC complexes.



Negative selection deletes dangerous T-cell clones

Self-antigen recognition may induce apoptosis in the thymus.

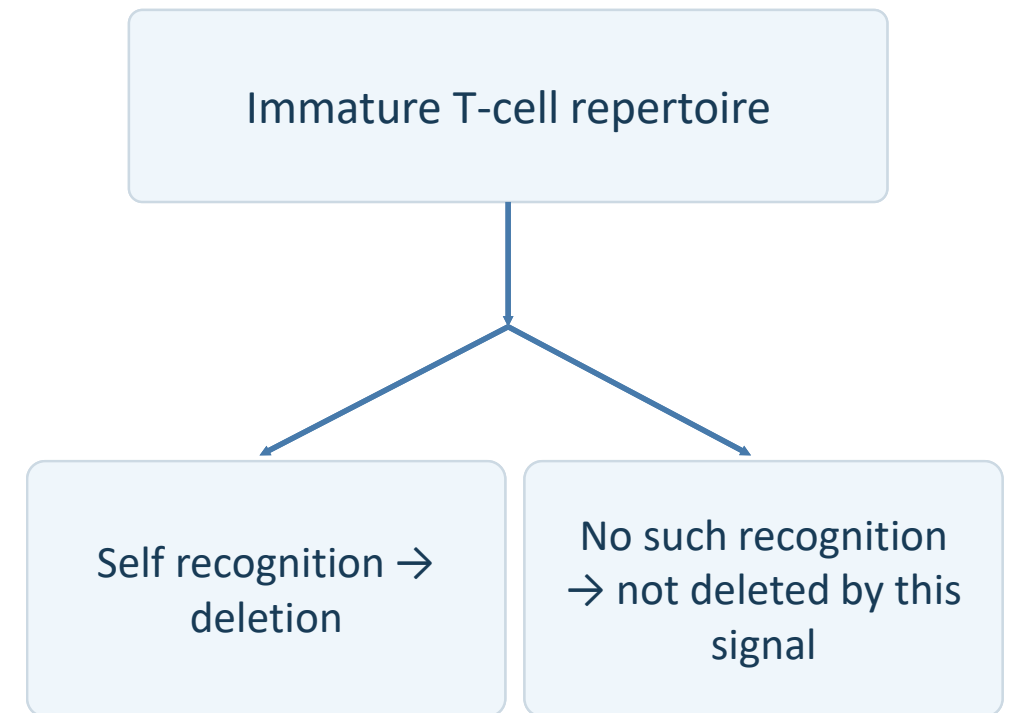
- A self-specific immature TCR receives signals upon antigen encounter.
- Those signals may culminate in programmed cell death.
- The mechanism is termed negative selection, or clonal deletion.



Negative selection is a clone-level filter

Specificity, rather than wholesale T-cell loss, is the central principle.

- Cells bearing receptors for encountered self determinants can be eliminated.
- Cells without that problematic recognition are not the target of that signal.
- The resulting mature pool is depleted of potentially injurious specificities.



Alternative outcomes

Apoptosis removes the receptor-bearing cell

Deletion differs from reversible loss of responsiveness.

- The autoreactive lymphocyte is physically eliminated by apoptosis.
- Its particular antigen receptor is consequently absent from surviving cells.
- Peripheral anergy, by contrast, can silence a mature cell without initial removal.

Clonal deletion

Cell eliminated by apoptosis

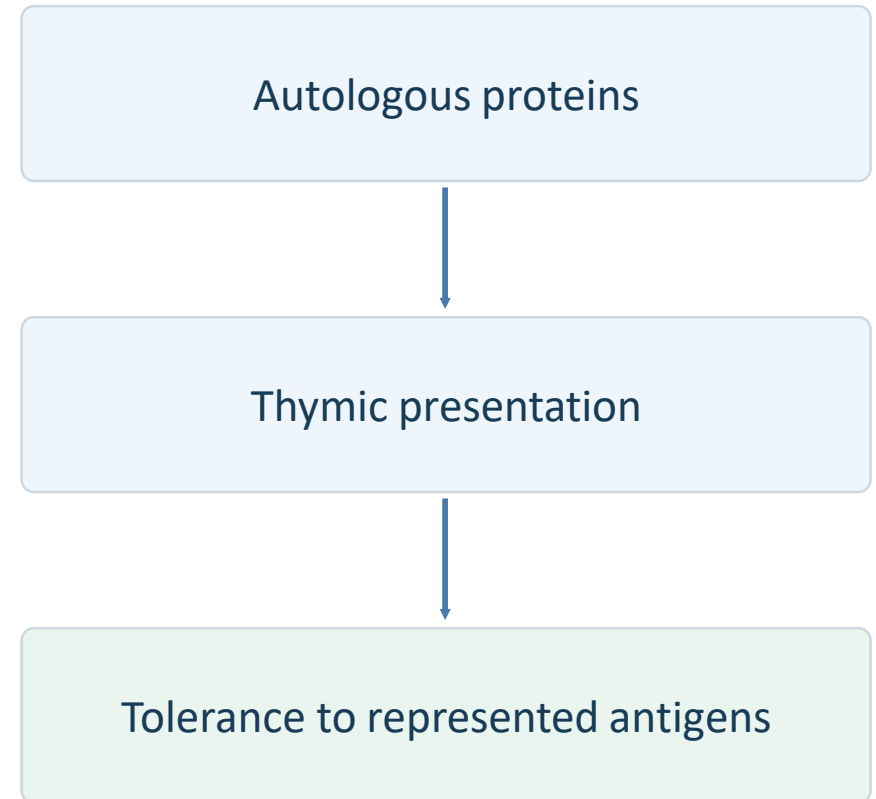
Anergy (peripheral)

Cell remains functionally unresponsive

Thymic antigen display is unusually broad

Selection requires more than thymus-specific antigens.

- Many different autologous proteins are processed in the thymus.
- The displayed antigen set includes some proteins usually associated with peripheral tissues.
- This broad representation allows deletion of clones threatening distant organs.



Tissue-restricted antigens create a sampling challenge

An endocrine or other peripheral antigen may rarely occur locally.

- A developing T cell can be selected only against antigen it encounters.
- Proteins ordinarily restricted to nonthymic tissues require thymic representation.
- Specialized expression mechanisms help bridge this anatomical separation.

Peripheral tissue

Normally expresses restricted antigen

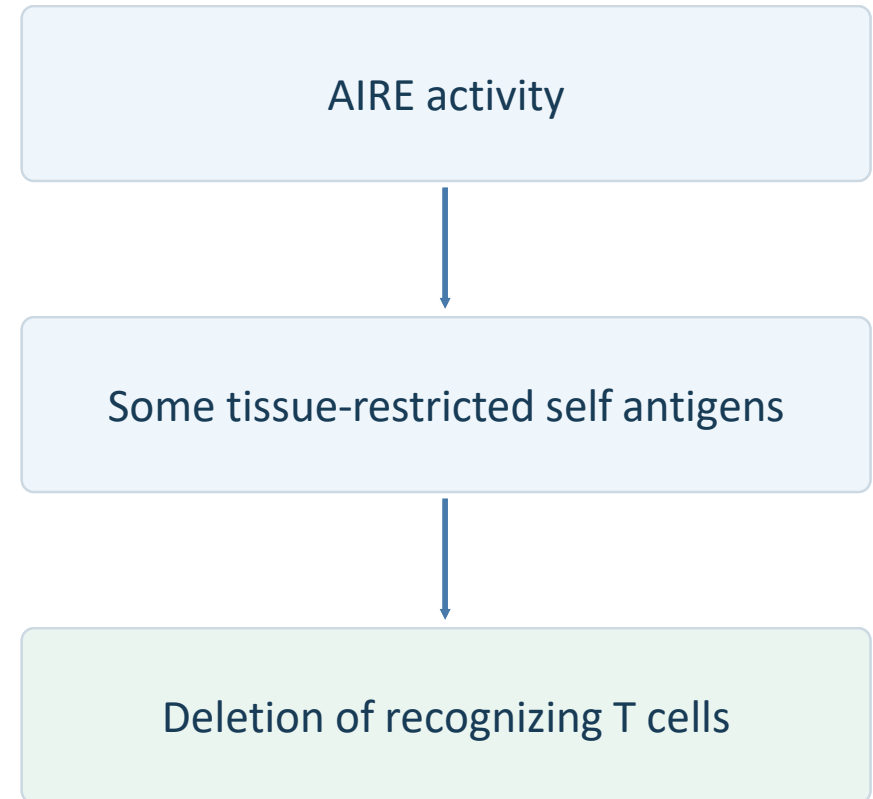
Thymus

Must display a relevant self determinant

AIRE broadens thymic self-antigen representation

AIRE is a key link between thymic selection and distant organs.

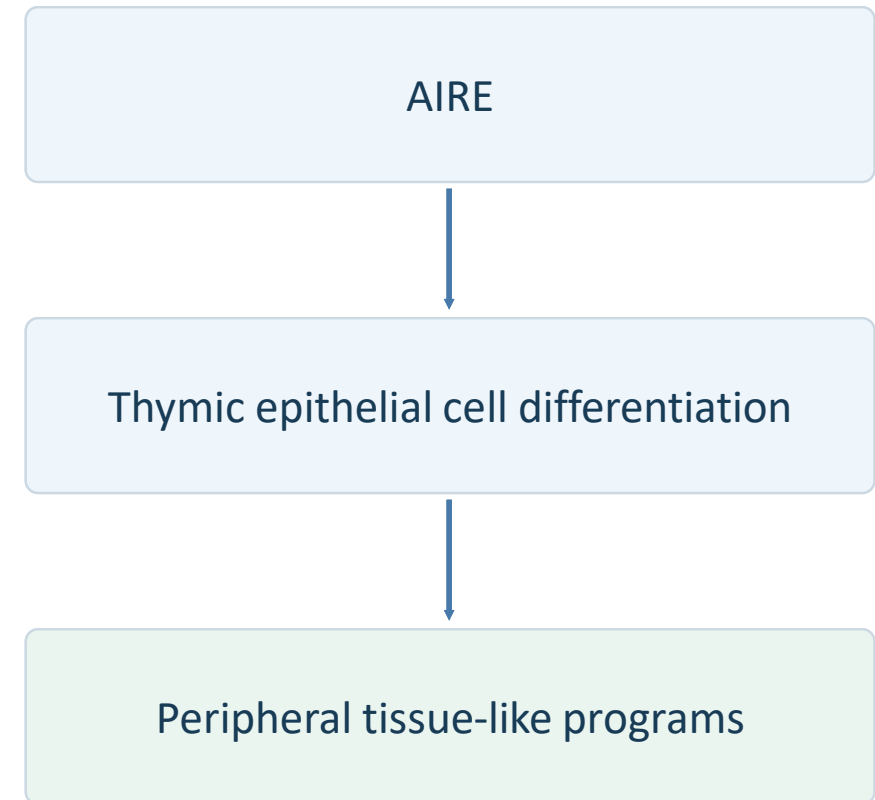
- AIRE means autoimmune regulator.
- It stimulates expression of some peripheral tissue–restricted self antigens within the thymus.
- The antigens can then contribute to elimination of self-specific immature T cells.



AIRE also influences thymic epithelial differentiation

AIRE is not limited to turning on a list of antigens.

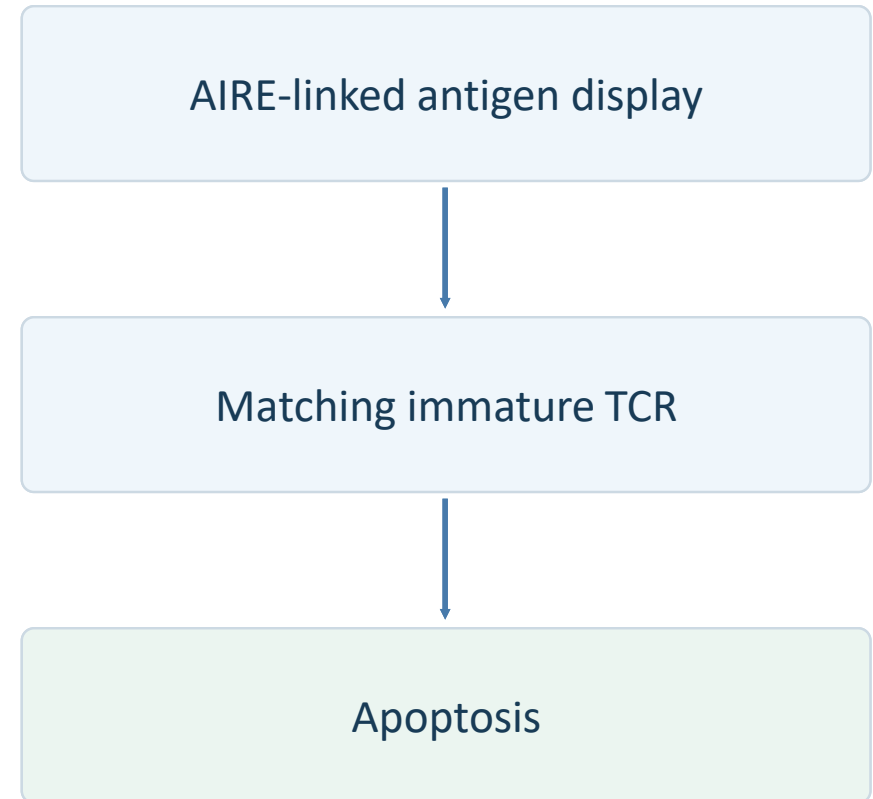
- AIRE also promotes differentiation of thymic epithelial cells.
- Some resulting cells mimic cells normally found in peripheral tissues.
- This increases the repertoire of host proteins encountered in thymic selection.



AIRE connects antigen availability to deletion

Central tolerance depends on both display and clone recognition.

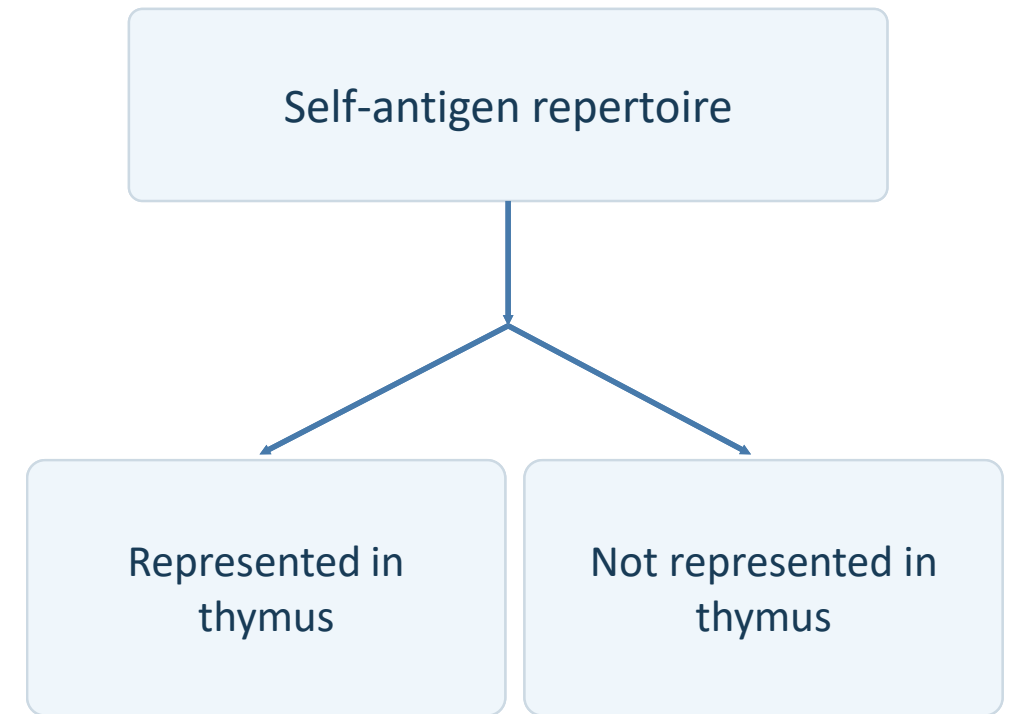
- AIRE-associated tissue antigens become available for thymic presentation.
- The matching self-reactive TCR can encounter these determinants.
- Deletion prevents that specificity from entering the mature pool.



AIRE does not imply universal thymic antigen display

Only some tissue-restricted antigens are induced.

- AIRE-dependent expression broadens but does not encompass every self antigen.
- Thymic antigen representation remains incomplete.
- AIRE therefore improves, but does not perfect, central tolerance.

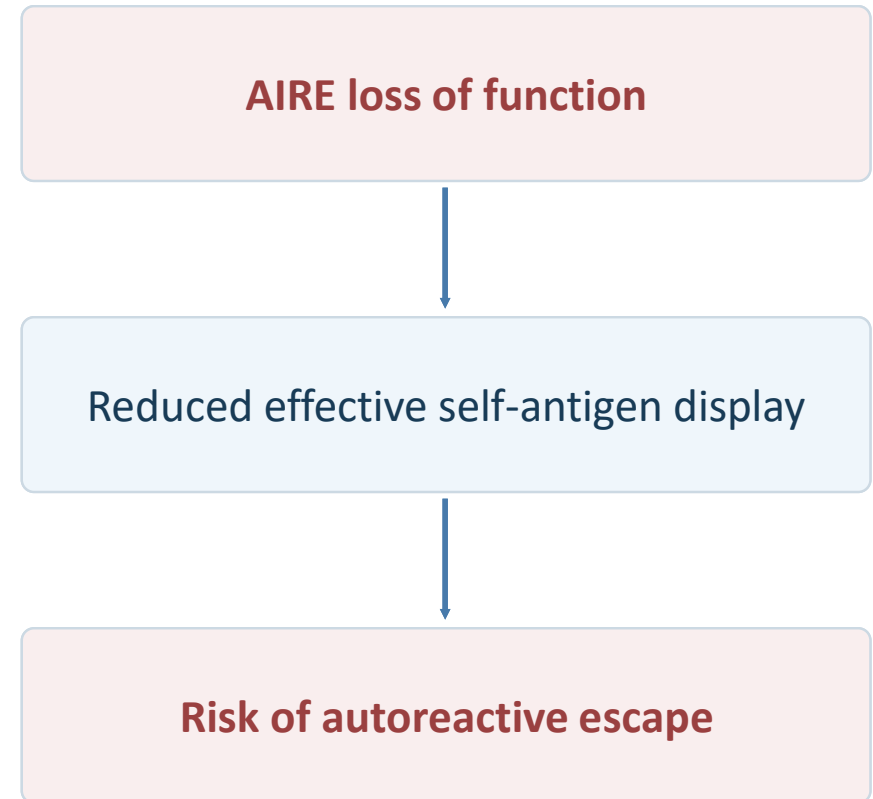


Alternative outcomes

AIRE loss disrupts a specific tolerance pathway

A genetic defect can remove a protective thymic mechanism.

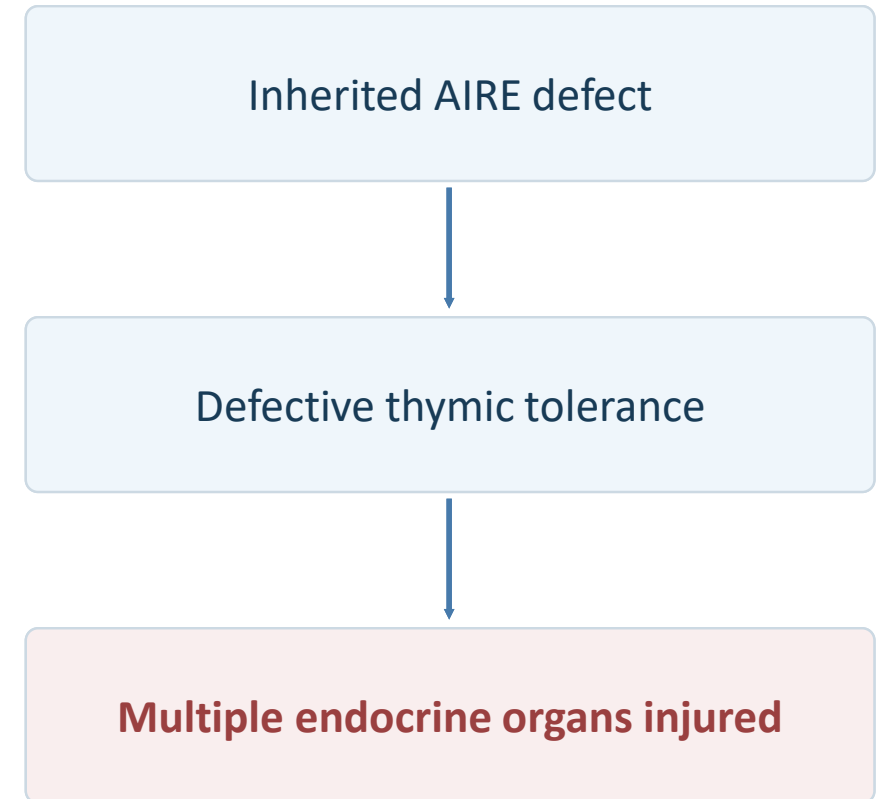
- Germline loss-of-function variants of AIRE impair the relevant pathway.
- Immature T cells specific for affected tissue antigens may fail to be deleted.
- The causal chain links defective thymic education with organ-directed autoimmunity.



AIRE deficiency has a human disease correlate

Endocrine autoimmunity illustrates failed central education.

- Rare patients with AIRE deficiency develop autoimmune polyglandular syndrome.
- Multiple endocrine organs may undergo immune-mediated destruction.
- The phenotype supports the physiological importance of thymic self-antigen display.



Autoimmune polyglandular syndrome is mechanistic evidence

A single tolerance pathway can influence several organs.

- The defect is in immune tolerance, not necessarily within each targeted gland.
- The affected endocrine organs provide a systemic readout of a central selection defect.
- This example is not evidence that all autoimmune diseases arise from AIRE mutations.

Primary defect

AIRE-dependent thymic selection

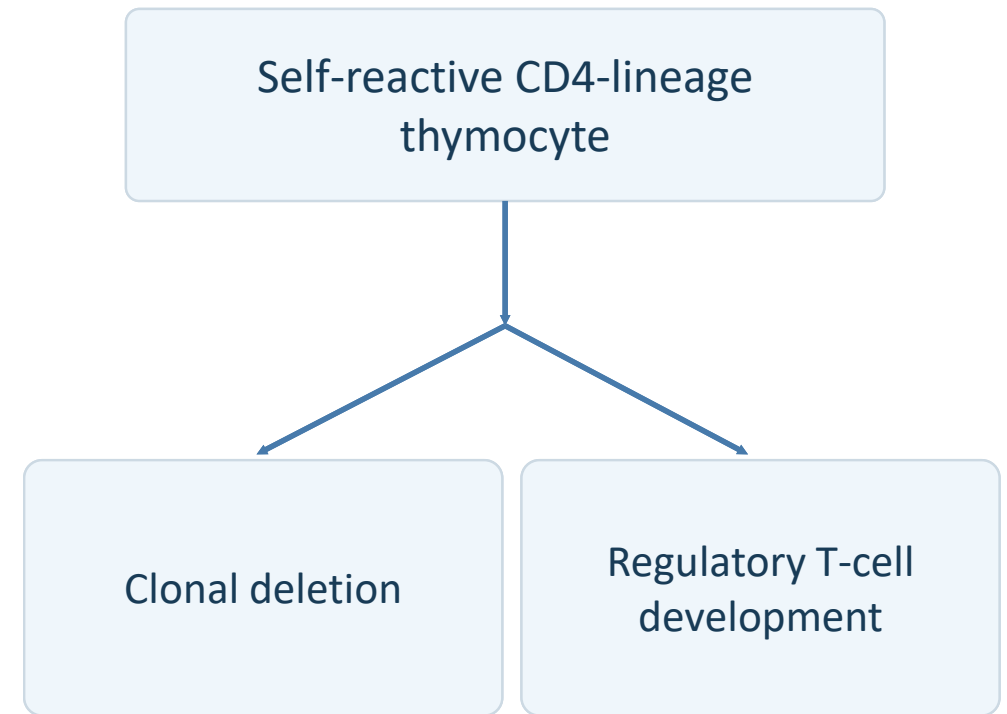
Downstream phenotype

Autoimmunity involving several endocrine organs

An alternative thymic fate is regulatory T-cell development

Not every CD4-lineage self-recognizing cell undergoes deletion.

- Some developing CD4 T cells recognizing self antigens become regulatory T cells.
- This lineage later suppresses immune responses, including responses to self.
- Thymic Treg generation is a productive outcome of selected self recognition.



Alternative outcomes

Thymic Tregs complement clonal deletion

Deletion and regulation prevent injury by different mechanisms.

- Deletion eliminates a developing clone that might otherwise be harmful.
- Regulatory T cells persist to restrain activity of other immune cells.
- Both outcomes can arise in connection with self-antigen recognition in the thymus.

Deletion

Remove a potentially dangerous clone

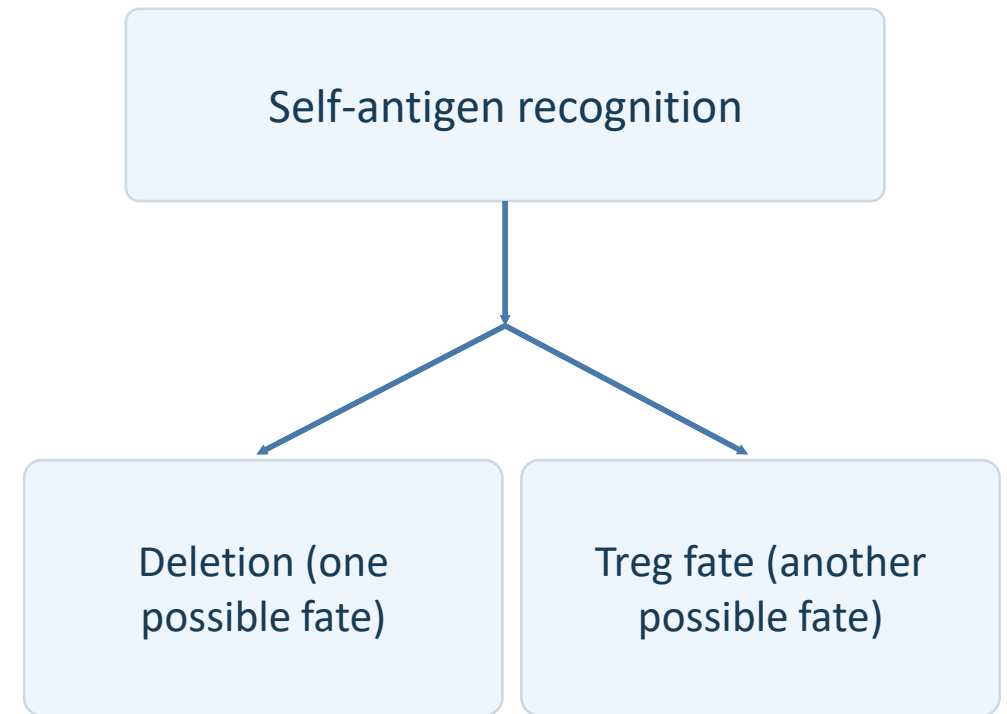
Treg development

Produce an immunosuppressive cell

The deletion-versus-Treg decision remains unresolved

The source does not establish a deterministic selection rule.

- The determinants of this thymic fate choice are not established.
- TCR affinity for thymic self antigens may contribute.
- It would be inaccurate to present a fixed affinity cutoff as an established rule.



Alternative outcomes

Affinity is a proposed influence, not a sole explanation

Avoid converting a hypothesis into an absolute pathway.

- The discussion identifies receptor affinity as a possible contributor.
- It does not state numerical affinity thresholds or exclusive determinants.
- The scientifically sound model leaves the fate decision conditional.

Established

Self recognition can cause deletion or Treg fate

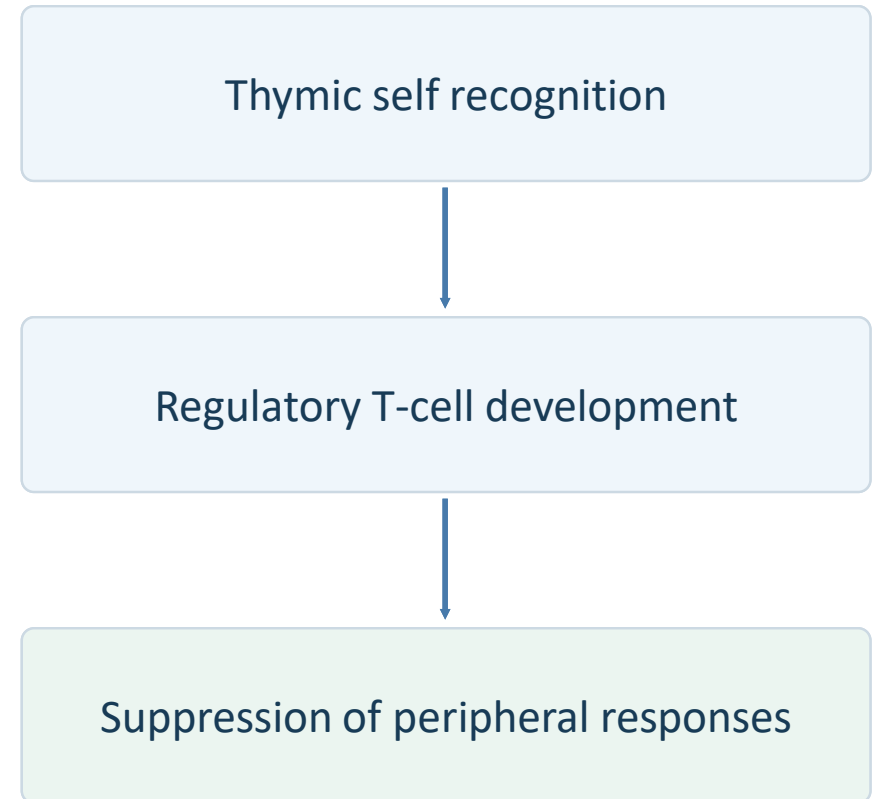
Unresolved

Exact rules governing the choice

Thymic regulatory cells provide peripheral protection

A central developmental event can yield a peripheral safeguard.

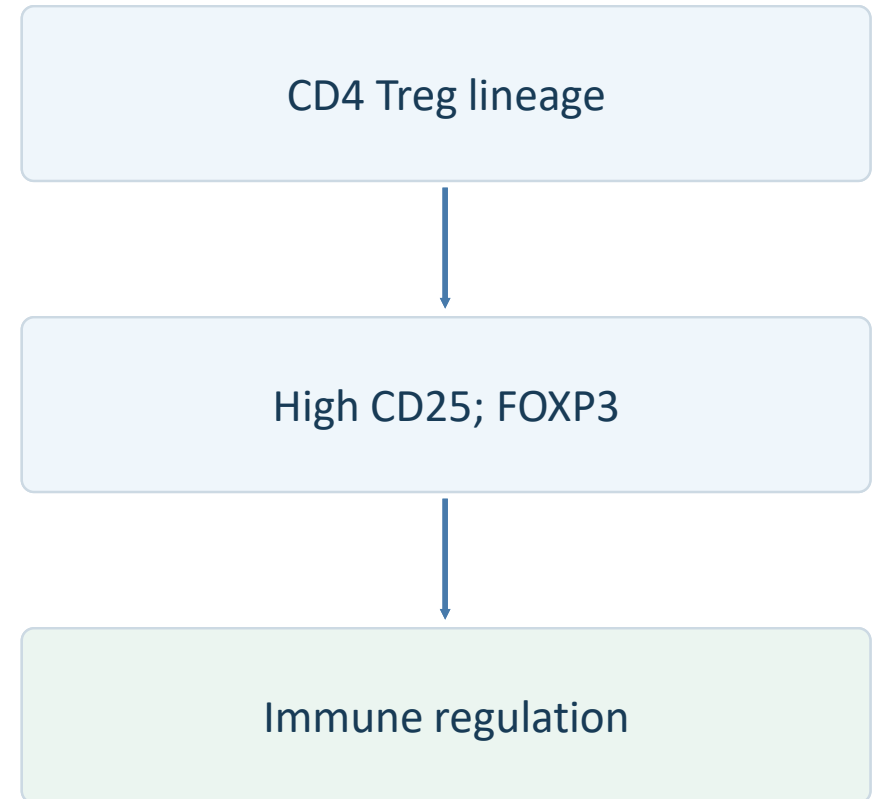
- Many regulatory T cells arise in the thymus after self-antigen recognition.
- Once mature, these cells suppress potentially harmful immune responses.
- Their origin is central; Their suppressive activity largely concerns peripheral responses.



FOXP3 and CD25 help identify the regulatory lineage

The regulatory lineage has a recognizable protein-expression profile.

- A well-defined regulatory population is CD4-positive and highly expresses CD25.
- FOXP3 is a transcription factor required for functional regulatory T-cell development.
- This phenotype describes the regulatory lineage, not the mechanism of thymic deletion.



Regulatory-cell deficiency offers a distinct failure mode

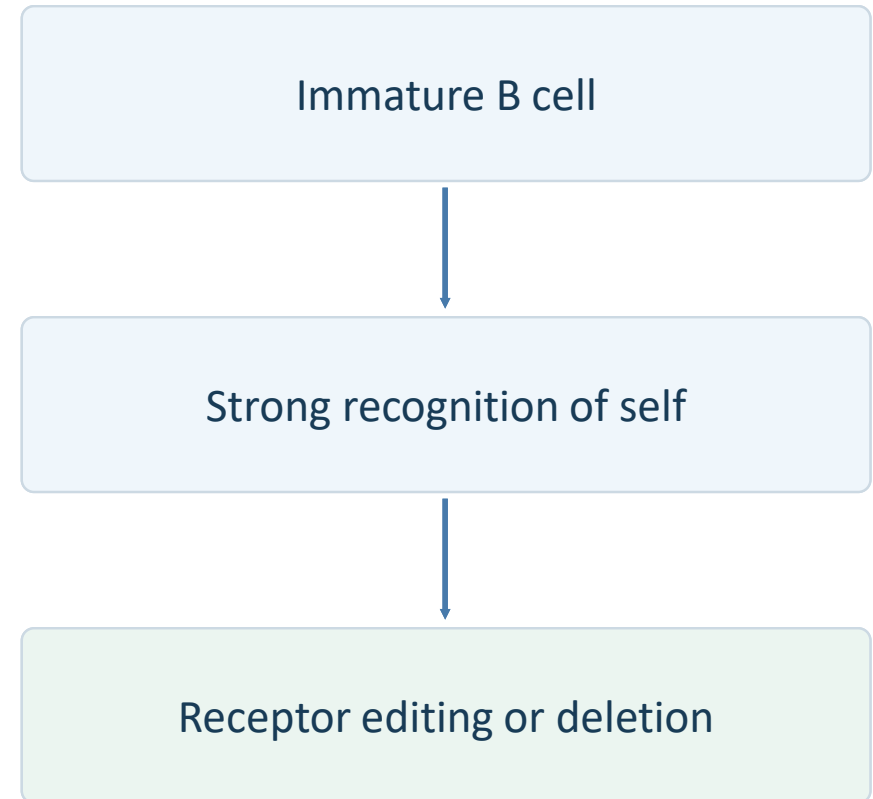
A regulatory defect is not synonymous with AIRE deficiency.

Feature	AIRE defect	FOXP3 defect
Primary pathway	Thymic antigen display	Regulatory T-cell function
Source-linked syndrome	Autoimmune polyglandular syndrome	IPEX
Teaching point	Deletion checkpoint impaired	Regulatory restraint impaired

Bone marrow is the B-cell checkpoint

Developing B lymphocytes are tested before entering the mature pool.

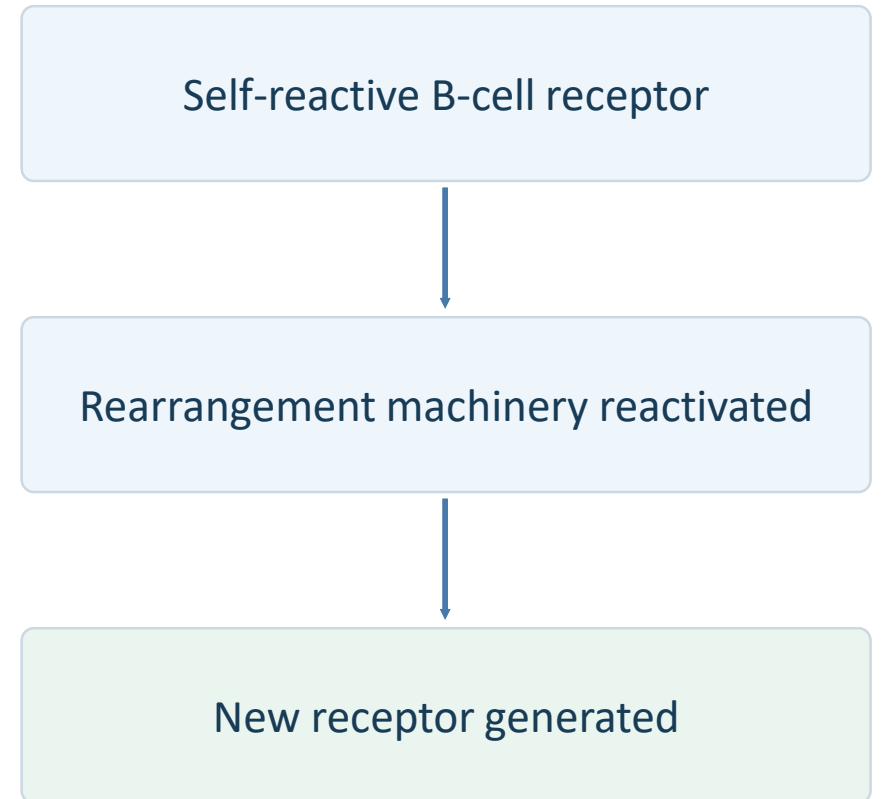
- Immature B cells express newly rearranged antigen receptors.
- Self-antigen recognition can reveal potentially autoreactive receptors.
- The bone marrow allows a response before those cells reach peripheral tissues.



Strong self recognition can reactivate rearrangement

Immature B cells have an additional corrective option.

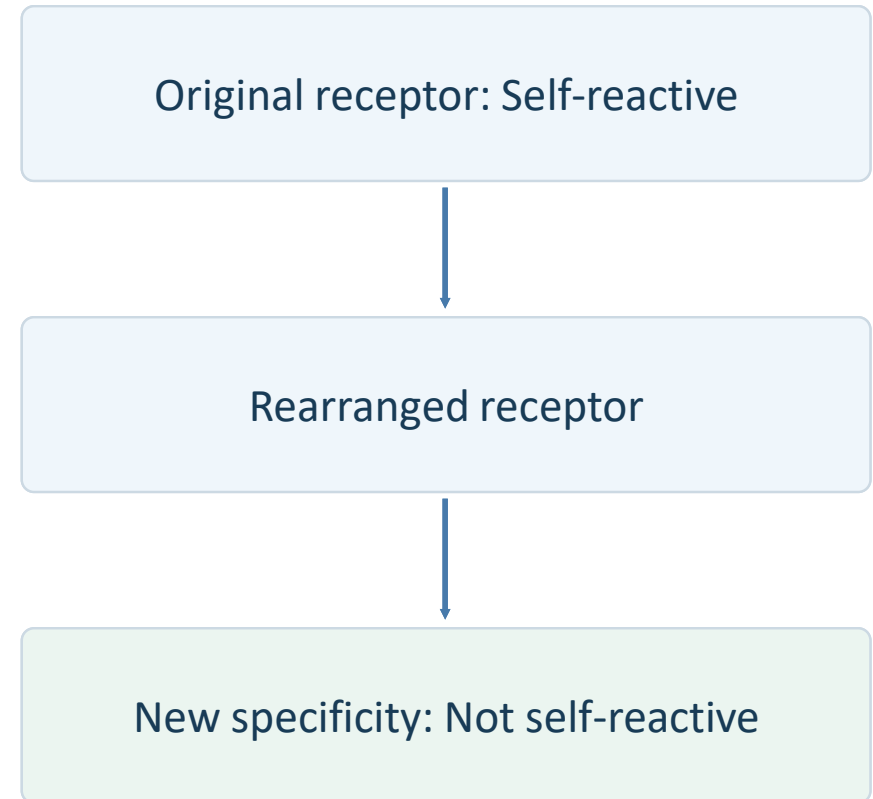
- Recognition of self antigen can restart antigen-receptor gene rearrangement.
- The cell can consequently express a different receptor.
- This is a defining feature of receptor editing.



Receptor editing changes specificity rather than cell identity

The same developing B cell can escape autoreactivity.

- The initial receptor recognizes a host antigen strongly.
- A subsequent rearrangement creates a new antigen receptor.
- If it is no longer specific for self, the cell need not be discarded for that reason.



Editing is a second chance for an immature B cell

Receptor revision preserves a useful developing cell.

- B-cell deletion eliminates a cell together with its receptor.
- Editing instead attempts to replace the dangerous specificity.
- The outcome is functional tolerance without obligatory loss of the clone.

Deletion

Discard cell carrying self-reactive receptor

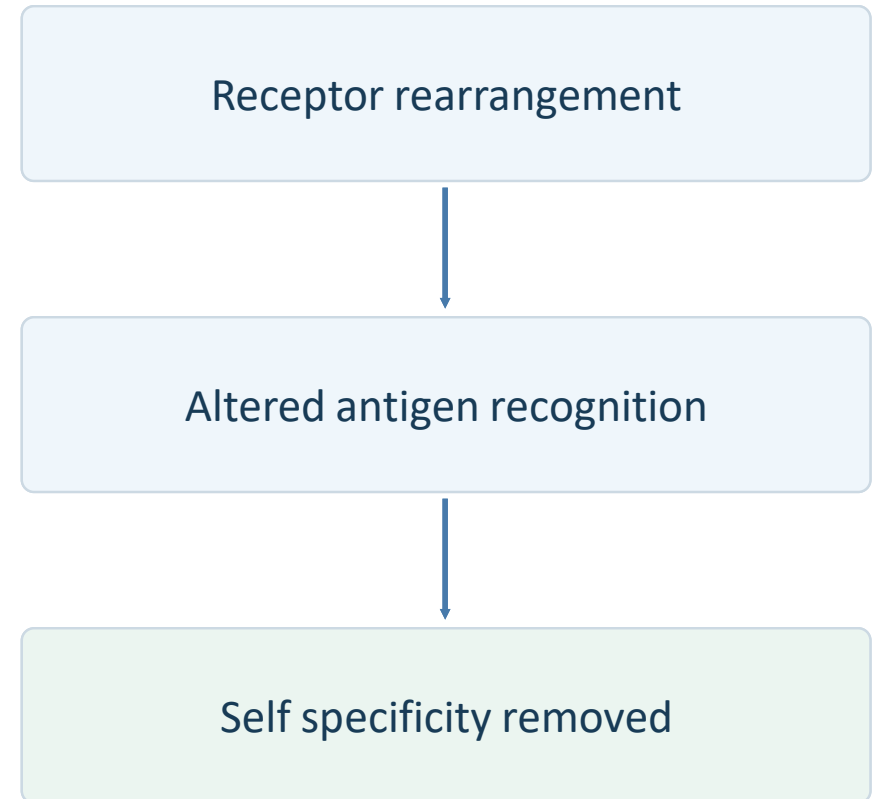
Editing

Replace receptor specificity within the cell

Successful editing requires loss of self specificity

A new receptor is valuable only if it corrects autoreactivity.

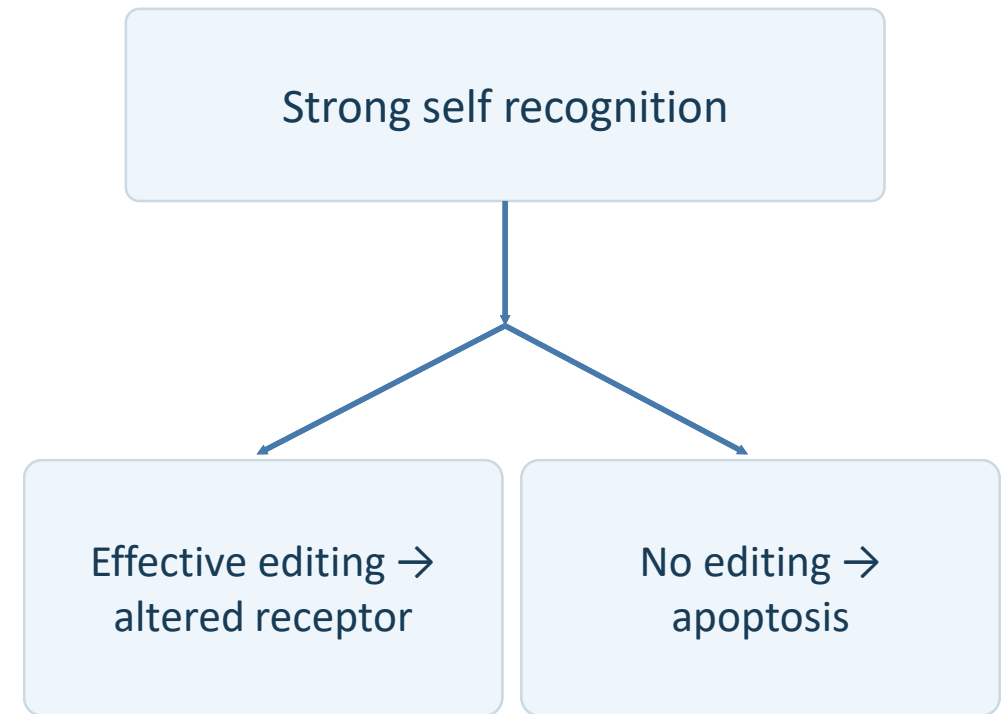
- Rearrangement must generate specificity different from the original self-reactive receptor.
- The edited receptor is described as no longer specific for self antigens.
- The tolerance outcome depends on changed recognition, not merely rearrangement itself.



Failure of editing results in deletion

Apoptosis is the fallback when autoreactivity remains.

- Some developing self-reactive B cells do not successfully edit their receptors.
- If receptor editing does not occur, the self-reactive cells undergo apoptosis.
- This removes potentially dangerous specificities from the mature B-cell pool.

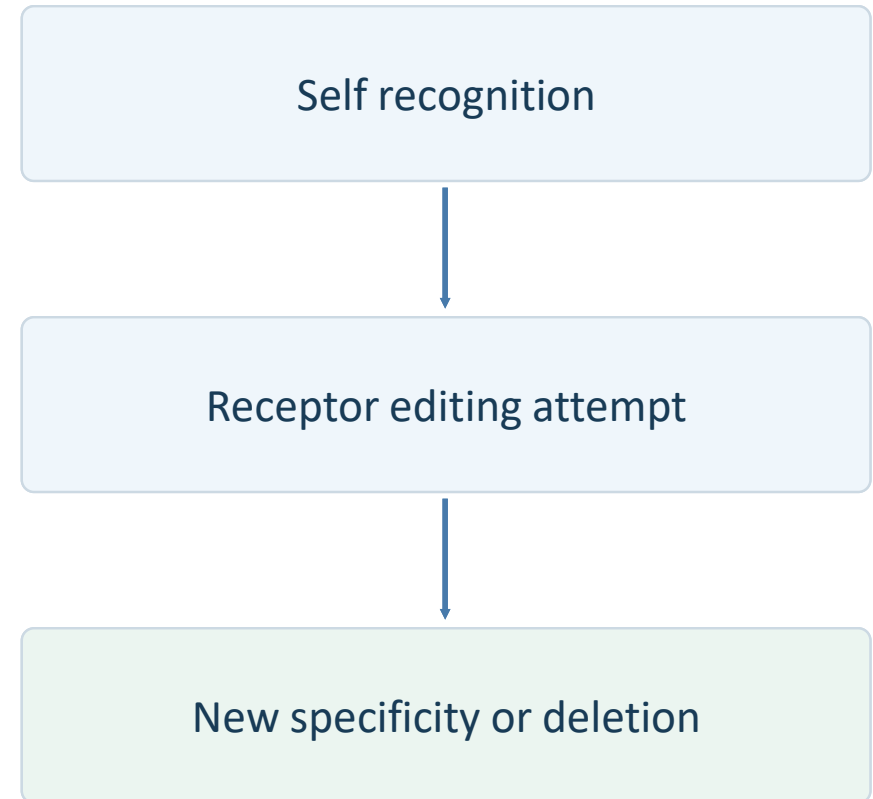


Alternative outcomes

The B-cell pathway is a sequence of decisions

Receptor revision precedes elimination in the described pathway.

- First, self antigen is recognized by an immature B cell.
- Second, receptor rearrangement may be reactivated.
- Third, the repertoire is shaped by successful editing or cell death.



Receptor editing is common during B-cell maturation

Editing is estimated to affect a substantial proportion of B cells.

- An estimated one-quarter to one-half of B cells may have been edited.
- This is a broad textbook estimate, not a universal rate for each B-cell subset.
- The point is that editing is a major physiological mechanism, not a rare anomaly.

Textbook estimate

About one-quarter to one-half of B cells

Interpretation

Editing contributes substantially to the normal repertoire

Receptor editing and T-cell deletion solve related problems

Both remove hazardous receptor specificity by different routes.

Aspect	Immature T cell	Immature B cell
Site	Thymus	Bone marrow
Response to self	Deletion; sometimes Treg fate	Editing; deletion if no editing
Mechanistic emphasis	Remove dangerous clone	Replace receptor when possible

Editing is not peripheral anergy

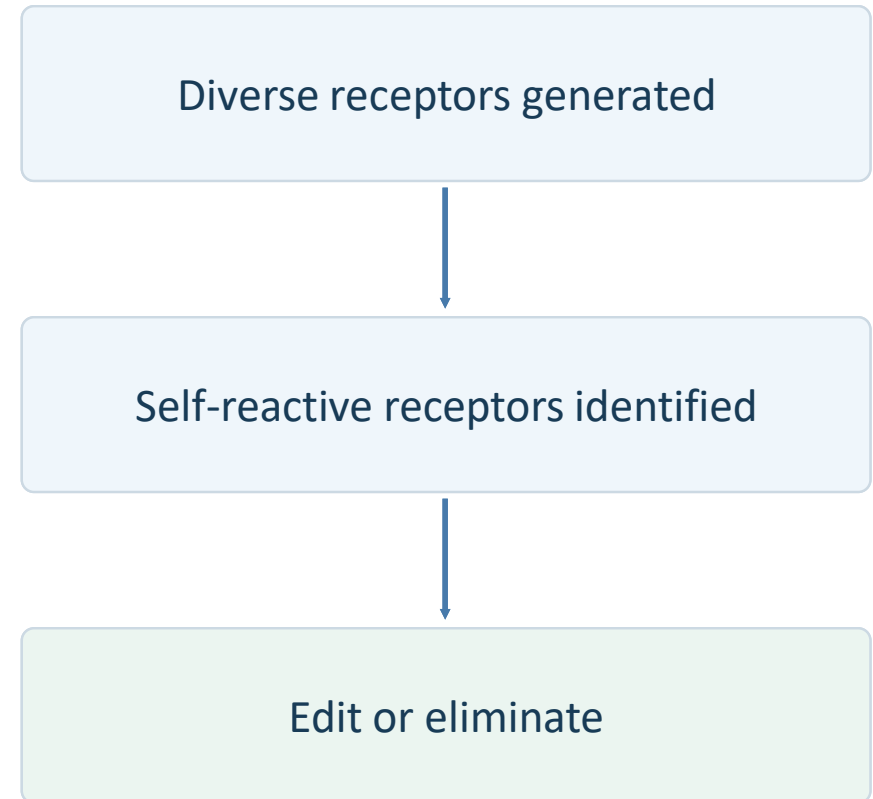
Three tolerance terms describe distinct mechanisms.

Mechanism	What changes?	Where emphasized?
Receptor editing	Antigen-receptor specificity	Immature B cells, marrow
Clonal deletion	Cell survival	Central T and B checkpoints
Anergy	Functional responsiveness	Peripheral tolerance

Receptor diversity requires both generation and correction

Immune competence and self-protection are coupled processes.

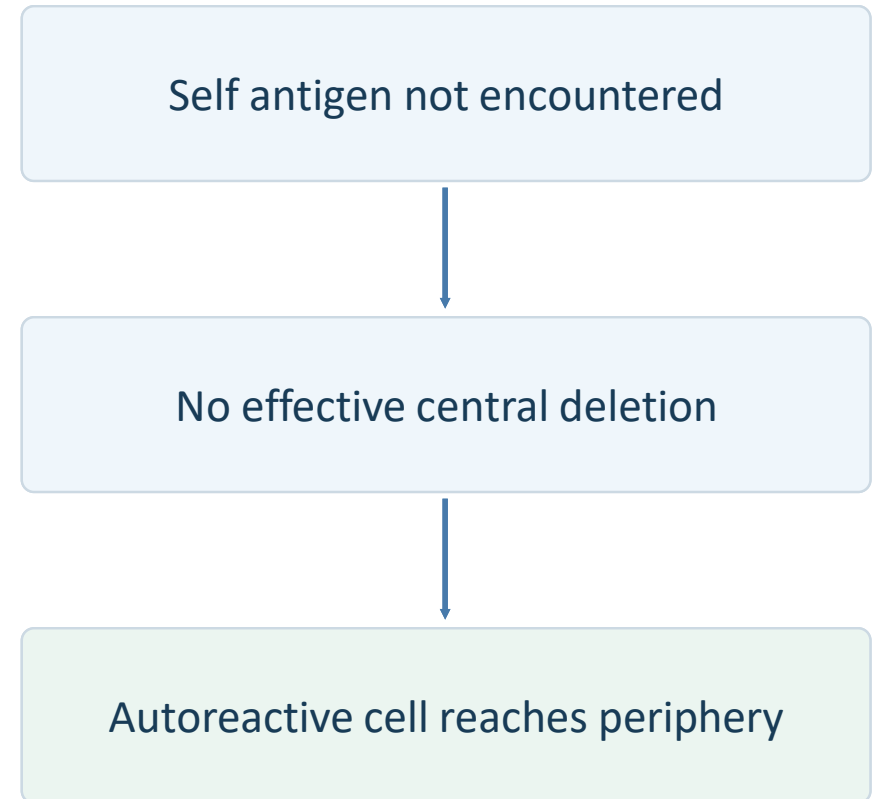
- Random rearrangement creates recognition breadth and the risk of autoreactivity.
- Editing provides a second rearrangement in selected self-reactive B cells.
- Apoptotic deletion prevents unsuccessful cells from contributing to mature immunity.



Central tolerance cannot test unseen antigens

Selection is constrained by which self antigens are represented.

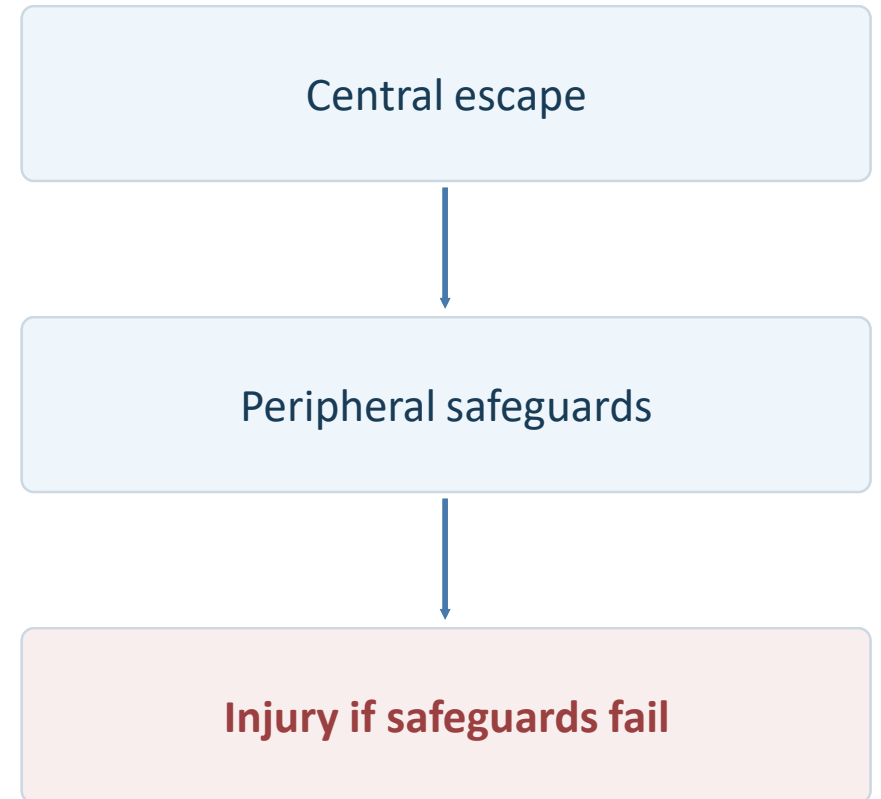
- Not every self antigen is available in the thymus and bone marrow.
- A cell can carry a receptor for a self antigen absent during its maturation.
- Such cells may escape into the mature repertoire despite normal selection.



Escape does not automatically produce autoimmune disease

A self-reactive cell is a risk, not synonymous with tissue injury.

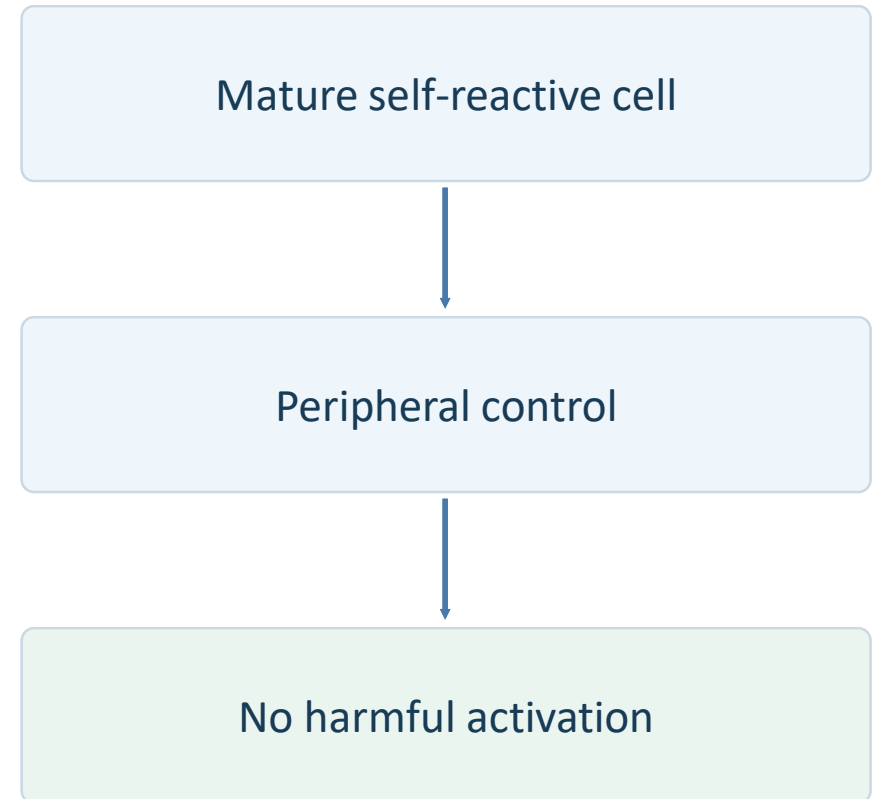
- Cells escaping central tolerance retain the potential to cause tissue injury.
- Other peripheral tolerance mechanisms may delete or silence them.
- Disease requires failure of sufficient protection against harmful responses.



Peripheral tolerance provides a second checkpoint

Mature self-reactive cells can still be restrained.

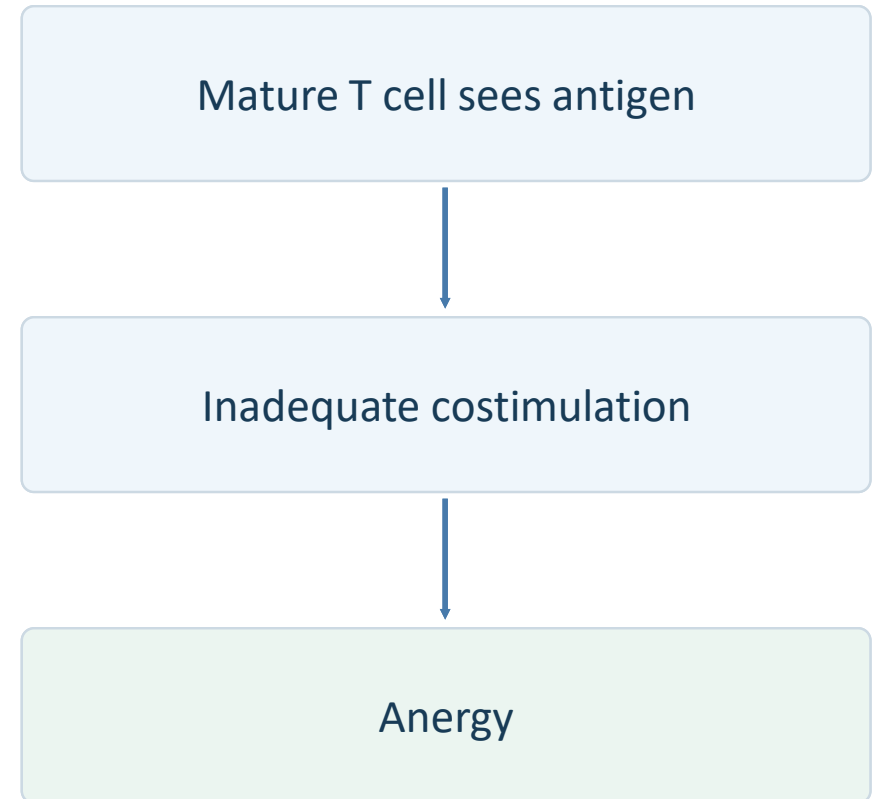
- Peripheral tolerance acts after lymphocytes reach peripheral tissues.
- Major safeguards include anergy, regulatory T-cell suppression, and apoptosis.
- These processes complement rather than replace thymic and marrow selection.



Anergy is functional silencing of a mature lymphocyte

Failure to receive adequate activation signals can prevent response.

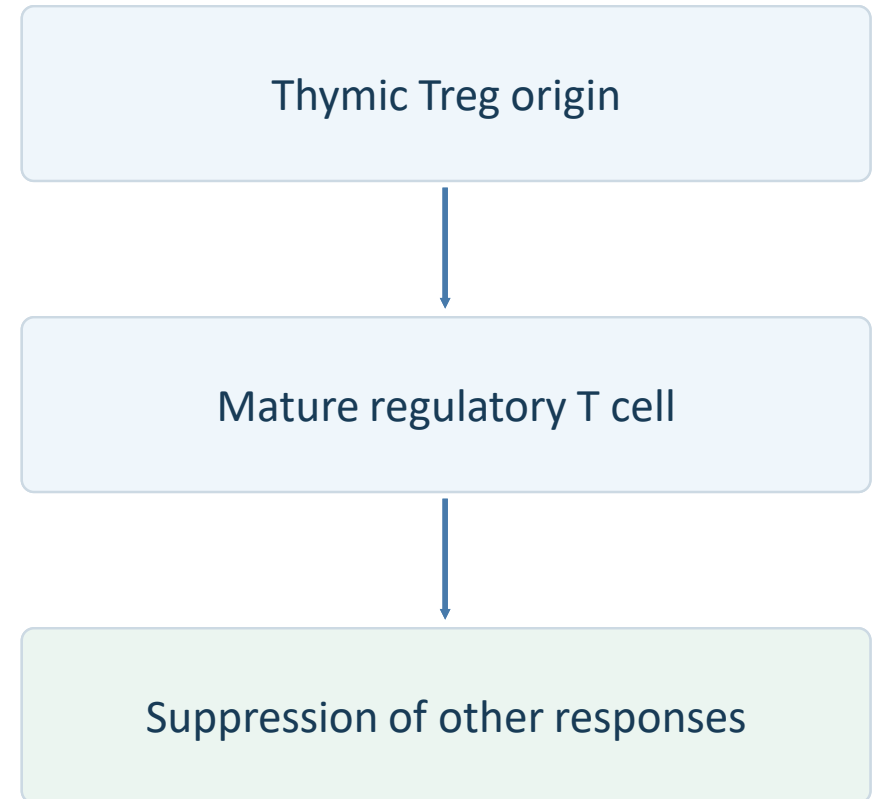
- Antigen recognition alone may be insufficient to activate a mature T cell.
- If antigen is presented without appropriate costimulation, the cell may become anergic.
- This is a peripheral mechanism, distinct from deletion during development.



Regulatory T cells suppress responses after thymic education

Developmental selection can generate a protective regulatory population.

- Thymic self-antigen recognition contributes to regulatory T-cell generation.
- Mature regulatory T cells restrain activation of other lymphocytes.
- Their suppressive role addresses potentially self-reactive cells in the periphery.



Peripheral deletion is not central negative selection

Similar endpoint; Different phase of lymphocyte life.

- Both processes may involve apoptosis of self-reactive cells.
- Central deletion takes place during immature lymphocyte selection.
- Peripheral deletion acts after maturation, when autoreactive cells encounter self.

Central deletion

Developing clone in thymus or marrow

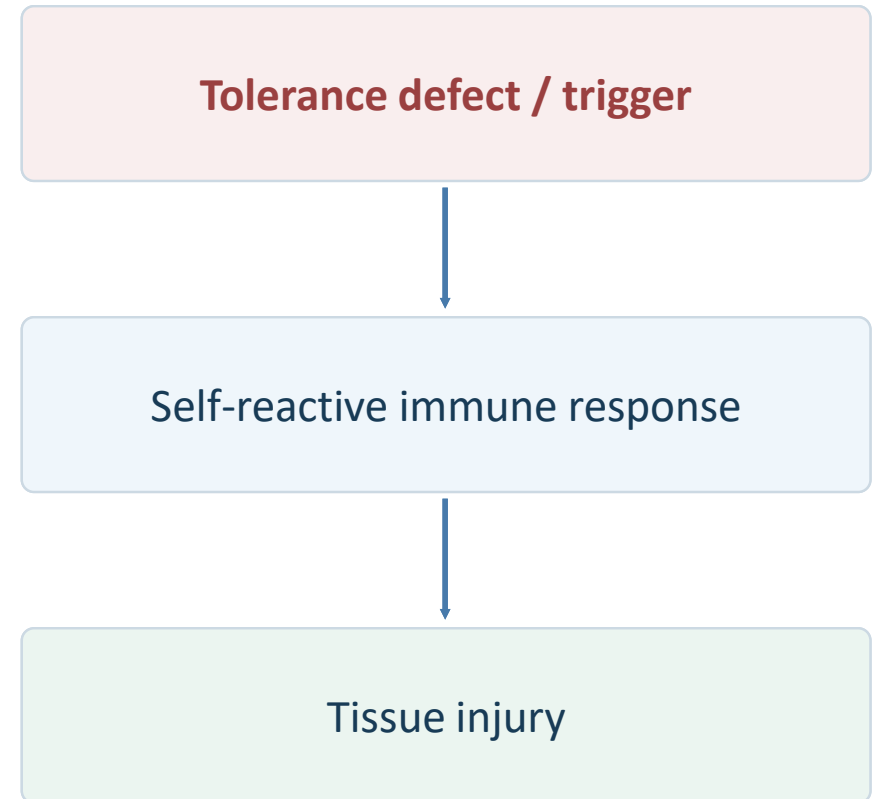
Peripheral deletion

Mature clone outside primary organs

Autoimmunity emerges when tolerance mechanisms fail

Breakdown can involve selection and/or later regulation.

- Autoimmune disease reflects immune attack on self antigens.
- Genetic susceptibility may disrupt distinct tolerance pathways.
- Infections or tissue injury can also favor exposure of self antigens and immune activation.



The mechanism of autoimmunity shapes its phenotype

Organ specificity depends on what the immune system targets.

- Responses directed at one organ yield organ-focused manifestations.
- Responses against widespread antigens can produce systemic disease.
- Central-tolerance defects contribute to risk but do not alone identify a target organ.

Organ-focused autoreactivity

Disease concentrated in a tissue

Widespread antigen targeting

Multi-organ disease

Mechanistic boundaries matter in slide interpretation

Do not transfer facts between stages without justification.

Concept	Central assignment	Do not conflate with
AIRE	Thymic antigen representation	All peripheral antigen display
Receptor editing	Immature B-cell receptor revision	T-cell deletion
Anergy	Peripheral functional silencing	Central apoptotic deletion

Clinical vignette: An inherited AIRE defect

A defined gene defect predicts a particular mechanism of tolerance failure.

- A patient has a germline AIRE loss-of-function mutation.
- The source associates this defect with autoimmune polyglandular syndrome.
- Question: Which checkpoint fails first—antigen representation or peripheral anergy?

Given

Germline AIRE loss of function

Reasoning

Impaired thymic presentation of some tissue antigens

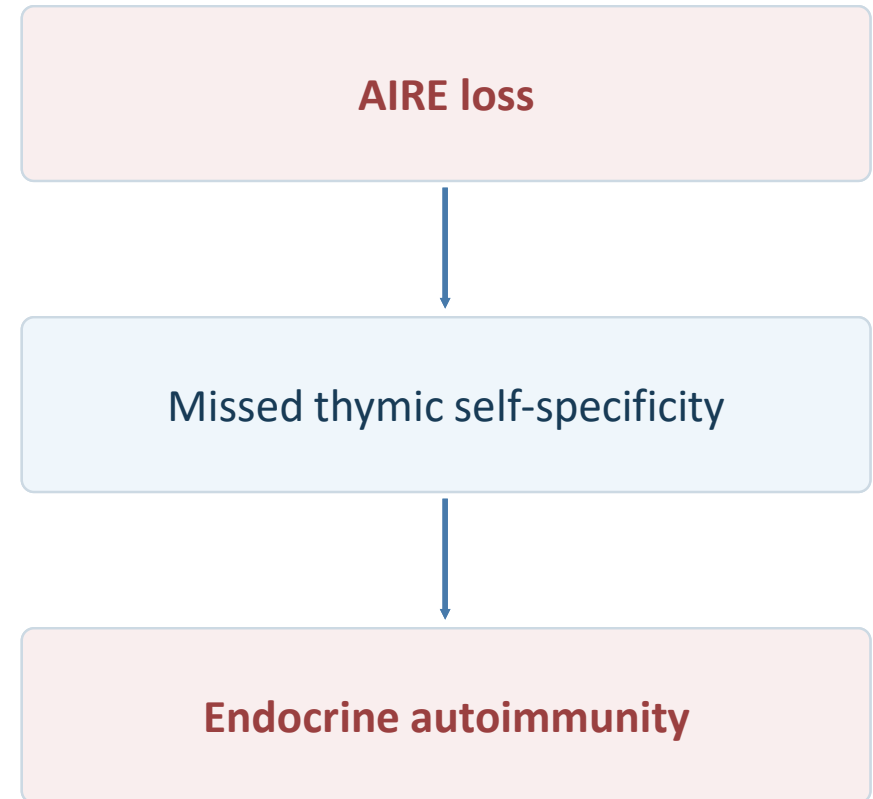
Inference

Self-reactive T cells may escape deletion

AIRE vignette: The mechanistic answer

The primary defect is inadequate central education.

- AIRE supports thymic expression of some tissue-restricted self antigens.
- Without this function, relevant thymic deletion becomes less effective.
- The clinical consequence can include immune injury to multiple endocrine organs.



Clinical vignette: A self-reactive immature B cell

Choose a developmental tolerance outcome from the cell type.

- An immature marrow B cell strongly recognizes a self antigen.
- Antigen-receptor rearrangement machinery is reactivated.
- Question: What result permits this cell to avoid self reactivity?

Cell

Immature B lymphocyte

Event

Strong self recognition

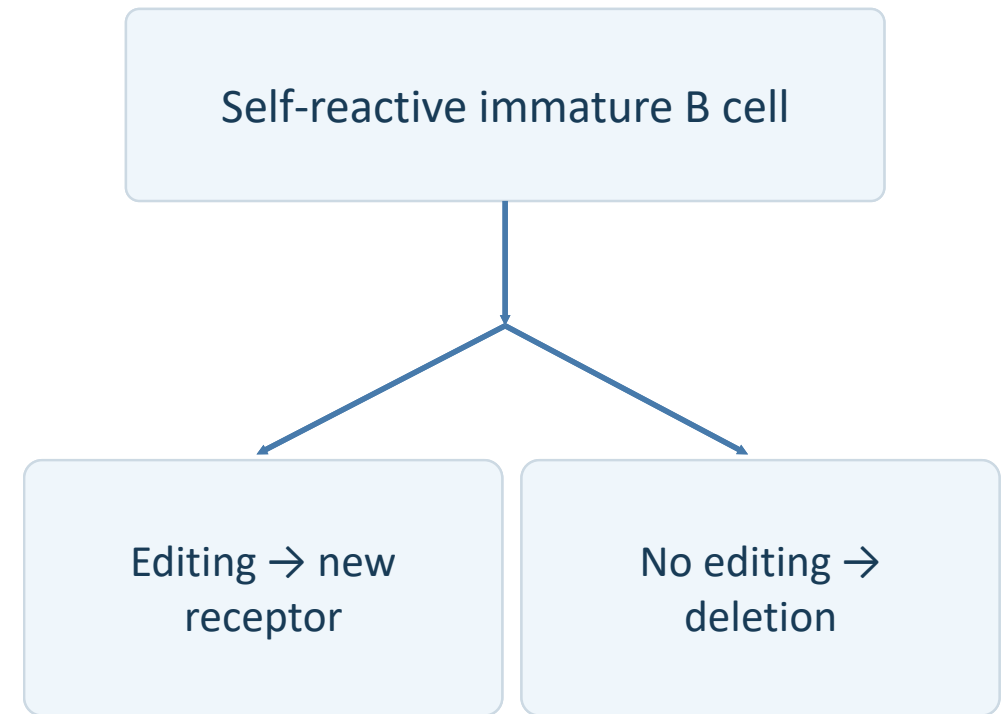
Required outcome

A different receptor not specific for self

B-cell vignette: Editing is the rescue mechanism

Changing the receptor removes the original problematic specificity.

- The developing B cell can generate a new receptor through editing.
- If the new receptor lacks self specificity, the dangerous recognition is removed.
- If editing does not occur, apoptosis as the alternative.



Alternative outcomes

Clinical vignette: Missing thymic self antigen

A normal receptor may evade deletion because the antigen is absent.

- An immature T cell can respond to a protein expressed in a distant tissue.
- Suppose that protein is not represented during thymic selection.
- Question: Can a clone specific for this antigen be guaranteed to be deleted?

Thymic presentation

Antigen absent

Central outcome

Relevant deletion cannot be assured

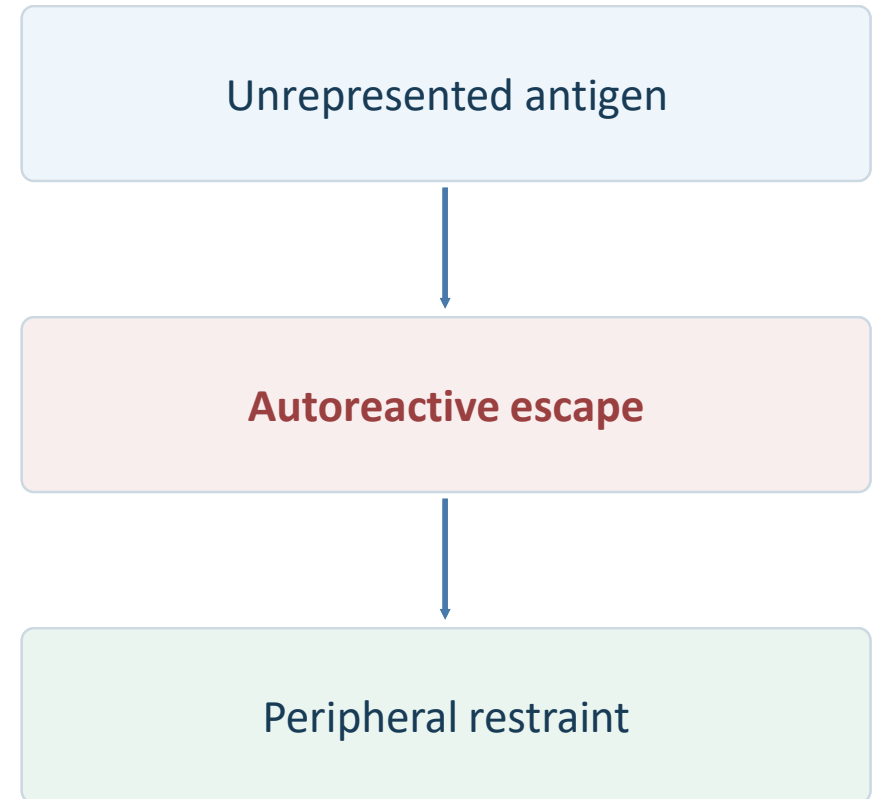
Next safeguard

Peripheral tolerance

Missing-antigen vignette: Peripheral backup is essential

Central tolerance cannot delete cells against unseen targets.

- The thymic selection process cannot respond to an antigen not encountered.
- A mature autoreactive clone can therefore enter peripheral tissues.
- Anergy, regulation, and deletion help prevent progression to injury.



Distinguish AIRE loss from FOXP3 loss

Both promote autoimmunity, but disrupt different steps.

Question	AIRE loss	FOXP3 loss
Primary biology	Thymic antigen display	Regulatory T-cell development/function
Central lesson	Defective clonal education	Defective immune restraint
Syndrome in source	Autoimmune polyglandular syndrome	IPEX

Assessment: Identify the developmental checkpoint

Three observations reveal three different tolerance outcomes.

Observation	Correct interpretation
Apoptotic immature T cell	Central negative selection
New B-cell receptor after rearrangement	Receptor editing
Self-recognizing CD4 cell becomes Treg	Thymic regulatory lineage

Assessment: Identify the statement that exceeds evidence

Mechanistic conclusions require correct qualification.

- Supported: AIRE promotes expression of some tissue-restricted antigens.
- Supported: Affinity may contribute to deletion-versus-Treg fate.
- Unsupported: All self antigens are displayed, or an exact TCR-affinity threshold is known.

Supported statement

Self presentation is broad but incomplete

Overclaim to avoid

Central tolerance eliminates every self-reactive lymphocyte

The central-tolerance pathway in one view

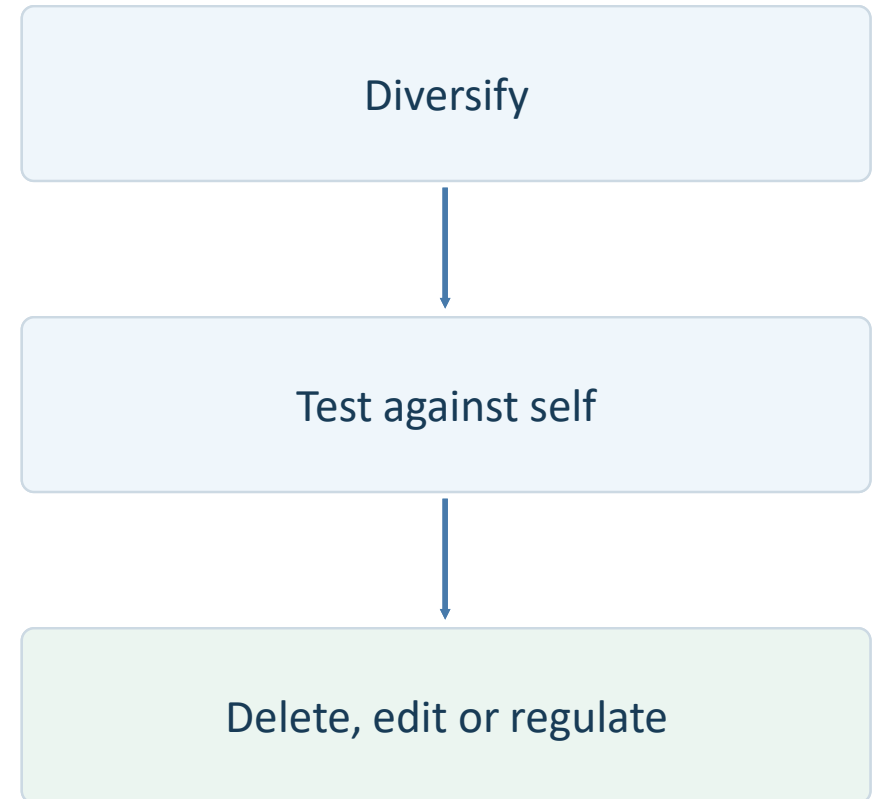
The major branch points differ between T and B maturation.

Checkpoint	Trigger	Major outcome
Thymus	TCR recognizes self peptide–MHC	Apoptosis; some CD4 Treg fate
Bone marrow	Immature BCR strongly recognizes self	Receptor editing or apoptosis
Periphery	Autoreactive mature cell escapes	Anergy / regulation / deletion

Five mechanistic conclusions

Central tolerance is a selective developmental safeguard.

- Receptor diversity inevitably creates potentially autoreactive specificity.
- Antigen representation and receptor recognition jointly determine selection.
- AIRE, thymic regulatory fates, and B-cell editing provide distinct protections.
- The system is incomplete and must be reinforced after maturation.



Learning check: Three discriminating questions

A correct explanation identifies lineage, site and cellular outcome.

- Which organ deletes many immature T cells recognizing self antigen?
- How can a strongly self-reactive immature B cell change specificity?
- Why can a self-reactive clone still reach peripheral tissues?

Model answers

Thymus; Receptor editing; Incomplete antigen representation

Clinical significance

Peripheral safeguards are needed to prevent injury

Primary reference

The diagrams and explanations are original teaching adaptations of the supplied chapter.

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026) · Chapter 6, “Diseases of the Immune System”

Central Tolerance and adjoining Immunologic / Peripheral Tolerance sections