

Peripheral Tolerance

Mechanisms of self-tolerance and the pathogenesis of autoimmunity

Mechanism-focused pathology lecture

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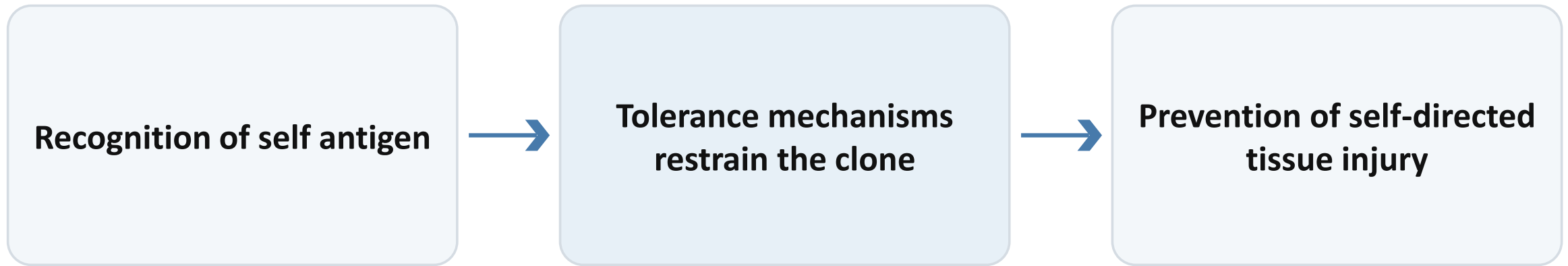
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Learning outcomes

- Explain why mature self-reactive lymphocytes need peripheral safeguards.
- Distinguish anergy, regulatory suppression, apoptotic deletion and sequestration.
- Relate CTLA-4, PD-1, FOXP3, IL-2, Bim and Fas to tolerance.
- Connect tolerance defects to illustrative autoimmune syndromes.

Self-tolerance protects normal tissues



Immunologic tolerance is antigen-induced unresponsiveness; Self-tolerance prevents immune attack on the host.

Central and peripheral tolerance differ

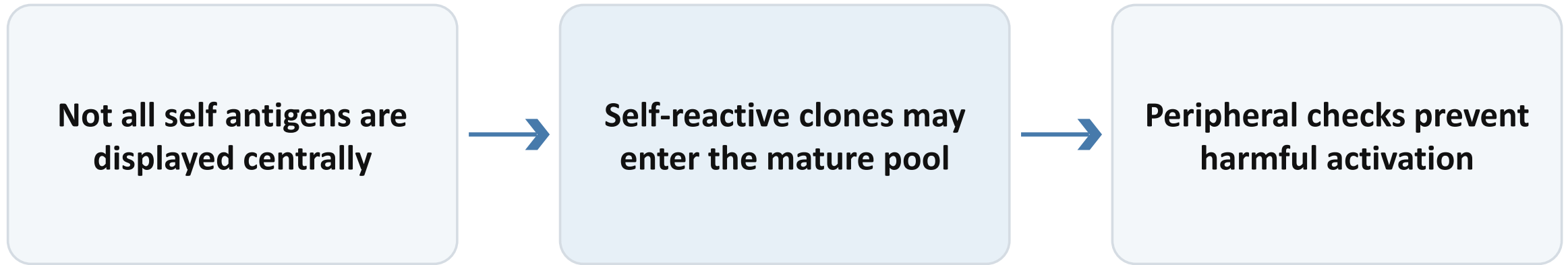
Central tolerance

- During lymphocyte maturation
- T cells: Thymus; B cells: Marrow
- Deletion or receptor editing; Some Tregs arise

Peripheral tolerance

- After mature cells enter tissues
- Acts on self-reactive cells that escaped
- Silencing, suppression, deletion or ignorance

Central tolerance is necessarily incomplete



Incomplete central antigen display leaves the need for peripheral tolerance.

Peripheral tolerance operates on mature cells

T lymphocytes

Best-characterized mechanisms

B lymphocytes

Can become anergic without helper T cells

Peripheral tissues

Self antigen is encountered outside primary lymphoid organs

Peripheral tolerance silences autoreactive T and B cells; Detailed mechanisms are best defined in T cells.

Four major peripheral safeguards

Anergy

Functionally inactive clone

Regulatory T cells

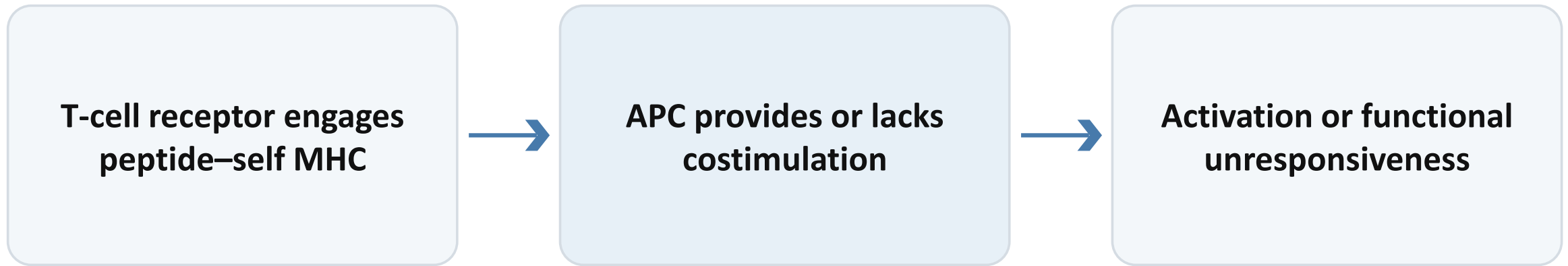
Active suppression of other
immune cells

Deletion / sequestration

Cell death or antigen kept
from immune recognition

The source outlines anergy, Treg suppression, apoptosis and antigen sequestration.

Antigen recognition alone is not enough



T-cell activation normally requires antigen recognition and APC-derived costimulation.

Signal 1 is antigen specificity

TCR recognizes peptide bound to self MHC on an APC

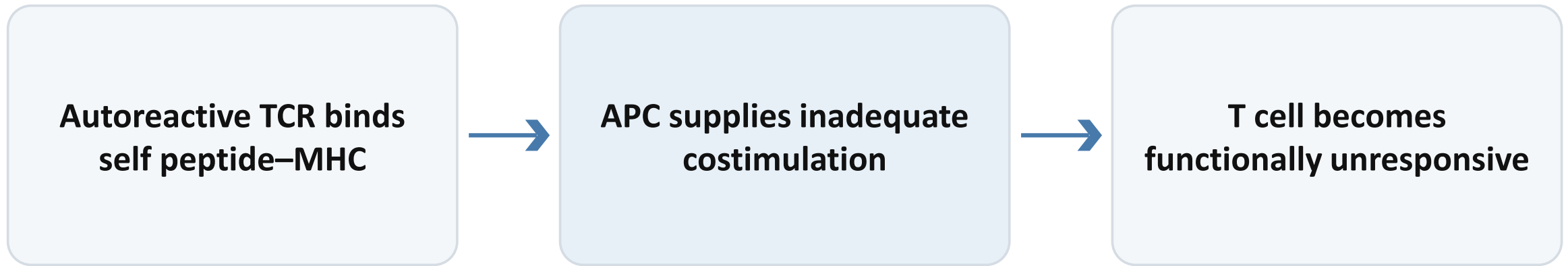
- This is necessary for antigen-specific responses.
- It does not, by itself, guarantee full activation.
- The fate depends in part on accessory signals.

Signal 2 is costimulation



CD28 engages APC B7-1 and B7-2 costimulators.

Self antigen without signal 2 causes anergy



Insufficient costimulation during self-antigen recognition can induce anergy.

Resting dendritic cells favor nonactivation

Resting DCs	Normal tissues	Consequence
B7 expression absent or weak	Autoreactive cells may encounter self antigen	Anergy instead of productive activation

The source links weak costimulation on resting dendritic cells to tolerance.

Activation and anergy are different fates

Productive T-cell response

- Antigen presented with adequate B7
- CD28 costimulatory engagement
- T-cell activation

Anergy

- Self antigen presented with weak B7
- Insufficient second signal
- No effective T-cell activation

Anergy is not the same as deletion

Anergy

- Clone remains functionally unresponsive
- Core event: Impaired response to stimulation

Deletion

- Self-reactive clone is eliminated
- Core event: Apoptosis

Inhibitory receptors reinforce tolerance



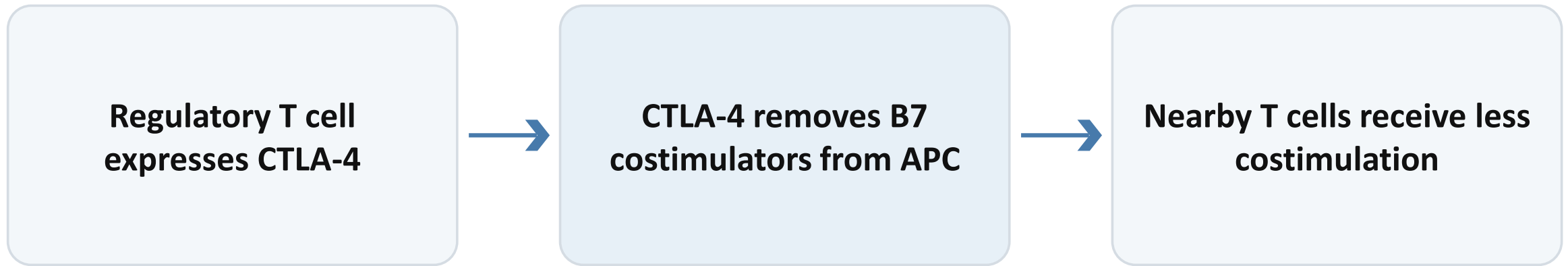
CTLA-4 and PD-1 are inhibitory checkpoints discussed in the source.

CTLA-4 targets the costimulatory axis

CD28	CTLA-4	Net effect
Binds B7 and supports costimulation	Also binds B7 molecules	Reduced access to the second signal

CTLA-4 binds the same B7 ligands as CD28 and promotes tolerance.

CTLA-4 removes B7 from antigen-presenting cells



The source describes CTLA-4-mediated removal of B7 by regulatory T cells.

CTLA-4 is prominent on regulatory T cells

Regulatory T cells are a major cellular setting for CTLA-4 activity

- Treg CTLA-4 helps prevent costimulation.
- Reduced B7 availability can promote anergy.
- This links active suppression to passive unresponsiveness.

CD28 versus CTLA-4: Opposed effects

Feature	CD28	CTLA-4
B7 binding	Yes	Yes
Principal effect	Costimulation	Limitation of costimulation
Tolerance relevance	Activation if signal 2 available	Promotes anergy / Treg suppression
Source emphasis	T-cell activation	Expressed mostly on Tregs

Both bind B7, but are contrasted by their functional effects.

PD-1 is a second inhibitory receptor



PD-1 blocks T-cell activation when engaged by its ligands.

PD-1 ligands are broadly distributed

PD-1

Coinhibitory receptor

PD-L1

One PD-1 ligand

PD-L2

Another PD-1 ligand;
Ligands occur on many cells

PD-L1 and PD-L2 are broadly expressed according to the source.

CTLA-4 and PD-1 have distinct described actions

CTLA-4

- Interacts with B7 on APCs
- Treg-associated removal of costimulators
- Reduces opportunity for signal 2

PD-1

- Engages PD-L1 / PD-L2
- Delivers an inhibitory signal
- Blocks T-cell activation

Checkpoint loss produces systemic inflammation



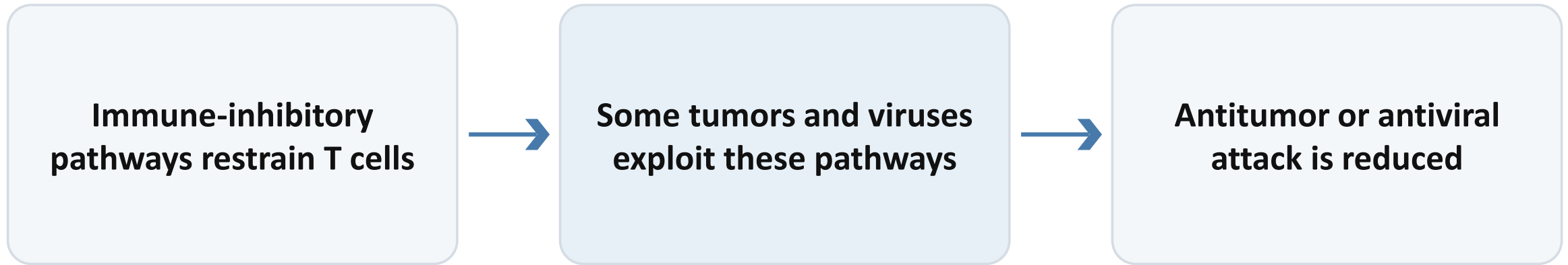
Knockout mouse and inherited human data support the importance of inhibitory checkpoints.

Human CTLA4 variants establish clinical relevance

Inherited CTLA4 mutations can cause systemic inflammatory disease

- This is human genetic evidence for checkpoint function.
- It supports a causal link between faulty inhibition and immune disease.
- It does not establish a mechanism for every common autoimmune illness.

Tumors and viruses can exploit immune brakes



The source states that tumors and viruses may use tolerance pathways to evade immune attack.

Checkpoint blockade releases inhibitory brakes



The source identifies antibody blockade of CTLA-4, PD-1 and PD-L1 as tumor immunotherapy.

The same checkpoint has opposite contexts

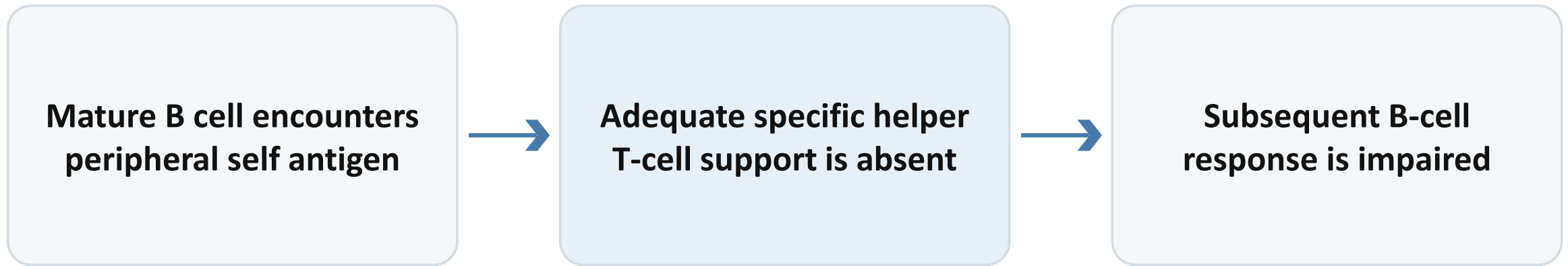
Normal self-tolerance

- Checkpoint intact
- Autoreactive activity restrained
- Protection from inflammation

Cancer immunotherapy

- Checkpoint blocked by antibody
- Antitumor immunity promoted
- Therapeutic release of restraint

Mature B cells also become anergic



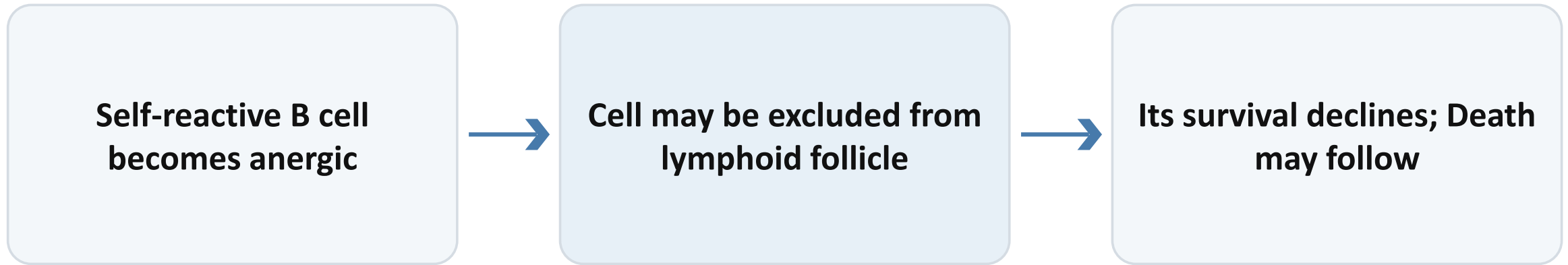
Peripheral self antigen can produce B-cell unresponsiveness, especially without helper T cells.

Absence of T-cell help matters to B cells

Self-antigen recognition	Helper-cell context	Outcome
B cell engages a self determinant	Specific helper T cells not available	An anergic B-cell state may develop

The source highlights missing specific helper T cells in B-cell anergy.

Anergic B cells may be excluded from follicles



The source links anergy to follicular exclusion and eventual B-cell death.

T- and B-cell anergy share a result

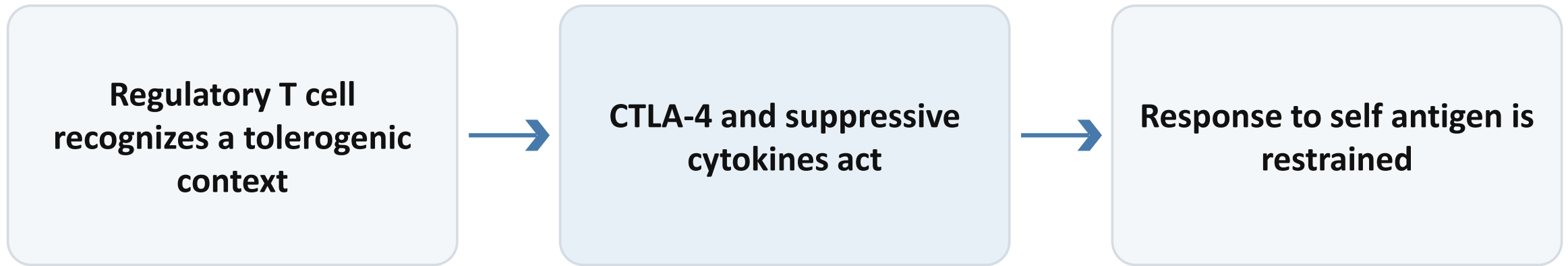
T-cell anergy

- Recognition with deficient costimulation
- CD28–B7 context central to explanation
- Functional T-cell unresponsiveness

B-cell anergy

- Self antigen without helper T-cell support
- Possible exclusion from follicles
- Unresponsiveness and possible death

Tregs actively suppress immune reactions



Tregs are a central peripheral suppression mechanism.

Regulatory T cells have two origins

Thymic development

- Many arise during recognition of self antigens
- Connects central selection with peripheral tolerance

Peripheral induction

- Tregs may also develop in peripheral lymphoid tissues
- Expands suppression outside the thymus

Best-defined Tregs are $\text{CD4}^+\text{CD25}^{\text{high}}\text{FOXP3}^+$

CD4

T-helper lineage phenotype

CD25

High IL-2 receptor α -chain
expression

FOXP3

Forkhead-family
transcription factor

The source defines the canonical Treg phenotype.

CD25 identifies the IL-2 receptor α chain



IL-2 and its receptor are required for functioning Treg populations.

IL-2 sustains regulatory T cells

IL-2 is essential for maintenance of regulatory T cells

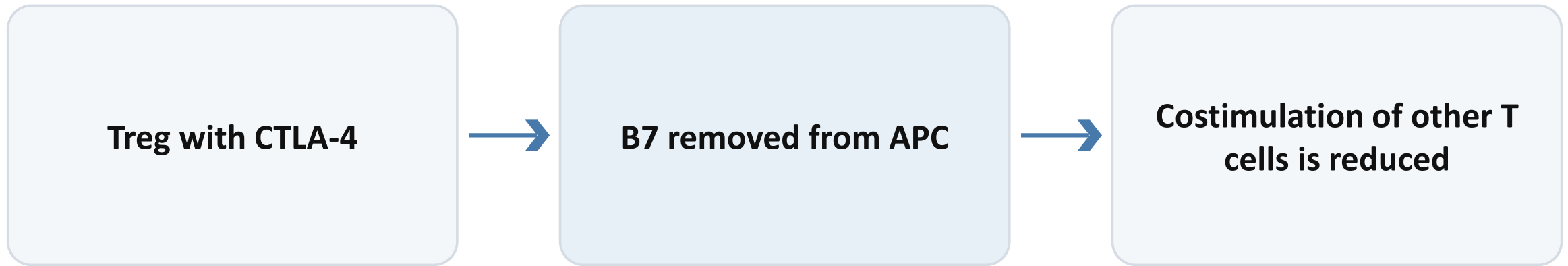
- Reduced IL-2 signaling can compromise immune regulation.
- The relevant receptor includes α - and β -chain components.
- This explains multiorgan autoimmunity in pathway defects.

FOXP3 is required for functional Tregs



FOXP3 is necessary for regulatory T-cell development and maintenance.

Tregs use CTLA-4 to limit costimulation



Regulatory T cells use CTLA-4 to inhibit T-cell costimulation.

Suppressive cytokines provide another pathway

IL-10

Immunosuppressive
cytokine

TGF- β

Immunosuppressive
cytokine

Consequences

Lymphocyte activation and
effector functions inhibited

The source describes IL-10 and TGF- β as possible mediators of Treg inhibition.

Treg suppression is multifactorial

Regulatory element	Described contribution
CTLA-4	Depletes APC B7 costimulators
IL-10	Inhibits immune activation / effectors
TGF- β	Inhibits immune activation / effectors
FOXP3 / IL-2	Required for regulatory-cell integrity

The suppressive phenotype is supported by distinct mechanisms.

FOXP3 loss causes IPEX



FOXP3 mutations cause immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome.

IPEX is a mechanism-linked syndrome

Immune dysregulation

Failure of immunologic
restraint

Polyendocrinopathy / enteropathy

Multi-organ autoimmune
involvement

X-linked

Included in the established
IPEX name

IPEX nomenclature and FOXP3 mechanism are explicitly given in the source.

IL-2 signaling defects can cause autoimmunity



The source identifies mutations in IL-2 or IL-2 receptor α/β as causes of autoimmune disease.

CD25 promoter associations are not causation

Observed association

- CD25 promoter polymorphisms
- Type 1 diabetes; Multiple sclerosis; Other autoimmune diseases

Interpretive limit

- Possible contribution of a Treg defect
- Association does not prove the pathway in every patient

Tregs protect tolerance beyond self antigens

Self antigens

Limit harmful autoreactivity

Fetal paternal antigens

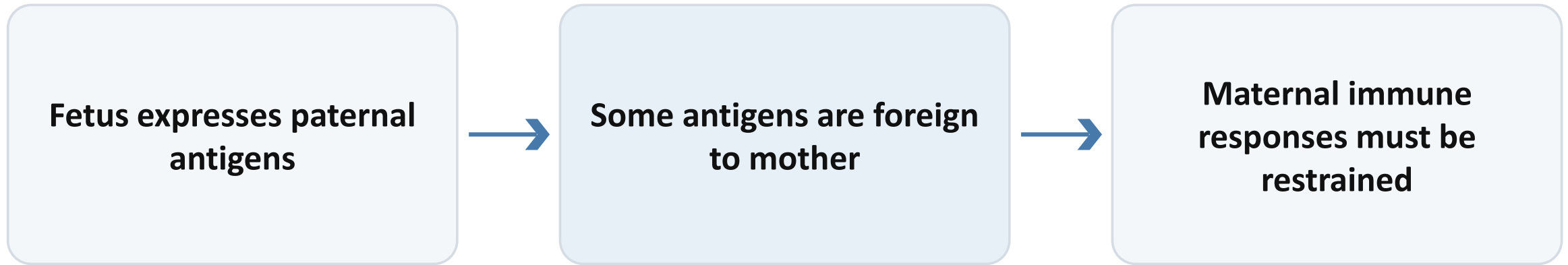
May help sustain maternal–
fetal tolerance

Commensal microbes

Help restrain responses to
resident microbes

The source identifies self, fetus and commensals as targets of Treg regulation.

The fetus presents a distinct tolerance challenge



Maternal–fetal tolerance is discussed as a physiological challenge.

Mouse experiments support fetal-antigen Tregs



The source attributes fetal-antigen Treg causality to experimental mouse studies.

Human pregnancy relevance remains unsettled

Established in cited experiments

- Mouse fetal-antigen FOXP3⁺ Tregs form
- Their depletion can cause fetal loss

Open in humans

- Contribution to normal pregnancy
- Whether Treg defects explain recurrent miscarriage

Deletion eliminates mature self-reactive T cells



Peripheral apoptotic deletion can remove self-reactive mature T cells.

Two apoptotic routes are proposed

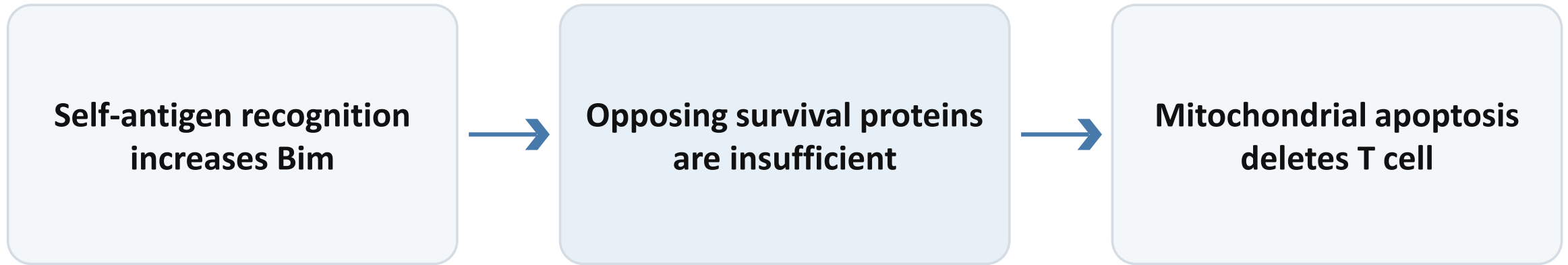
Mitochondrial pathway

- Bim becomes unopposed
- Intrinsic apoptosis occurs

Death receptor pathway

- Fas engages FasL
- Extrinsic apoptosis occurs

Bim promotes mitochondrial apoptosis



Unopposed Bim may induce deletion via the mitochondrial pathway.

BCL-2 and BCL-X counteract Bim

Bim

Pro-apoptotic BCL-family
member

BCL-2 / BCL-X

Anti-apoptotic family
members

Balance

Without full activation, Bim
may dominate

The source contrasts Bim with BCL-2 and BCL-X induction during full lymphocyte activation.

Full activation favors survival signaling

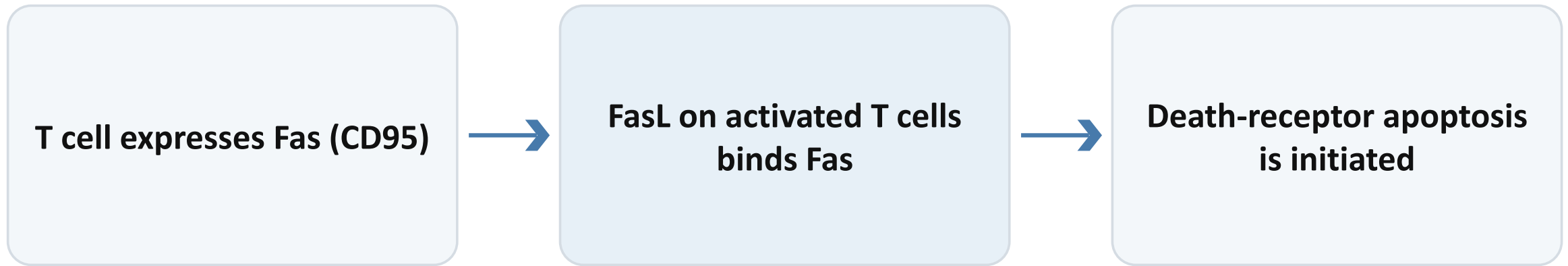
Full activation signals

- Anti-apoptotic BCL proteins can be induced
- Survival of responding T cells supported

Self recognition without full support

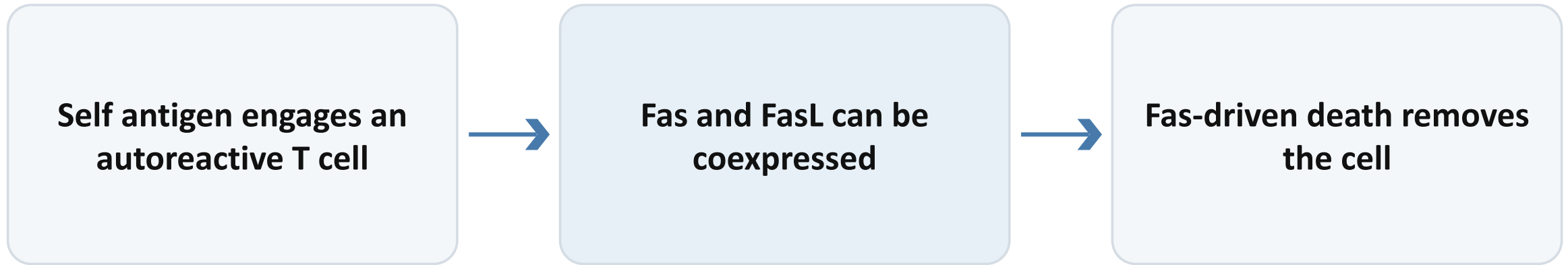
- Bim activity may remain unopposed
- Clonal deletion becomes possible

Fas and FasL form a death receptor pathway



The source names Fas/CD95 as TNF-family death receptor and FasL as its ligand.

Fas-mediated deletion can be self-directed



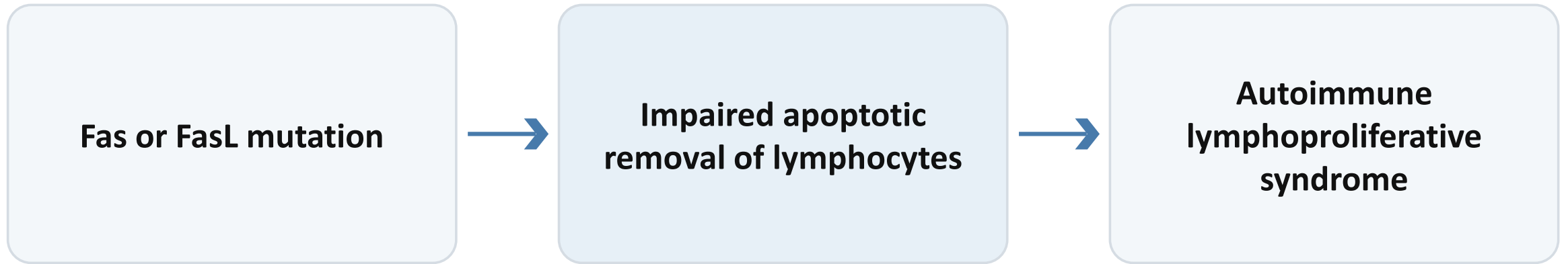
Self-antigen engagement can produce Fas/FasL coexpression and apoptotic elimination.

Fas and Bim are not interchangeable

Feature	Bim pathway	Fas pathway
Trigger described	Unopposed pro-apoptotic Bim	Fas–FasL engagement
Route	Mitochondrial (intrinsic)	Death receptor (extrinsic)
Important members	Bim, BCL-2, BCL-X	Fas/CD95, FasL
Teaching context	Peripheral T-cell deletion	Peripheral T-cell deletion

Both pathways contribute to proposed apoptotic elimination.

Fas pathway defects cause ALPS



ALPS, with lupus-like features, is described following Fas / FasL mutations.

ALPS links failed deletion to disease

Molecular defect

Fas or FasL

Cellular consequence

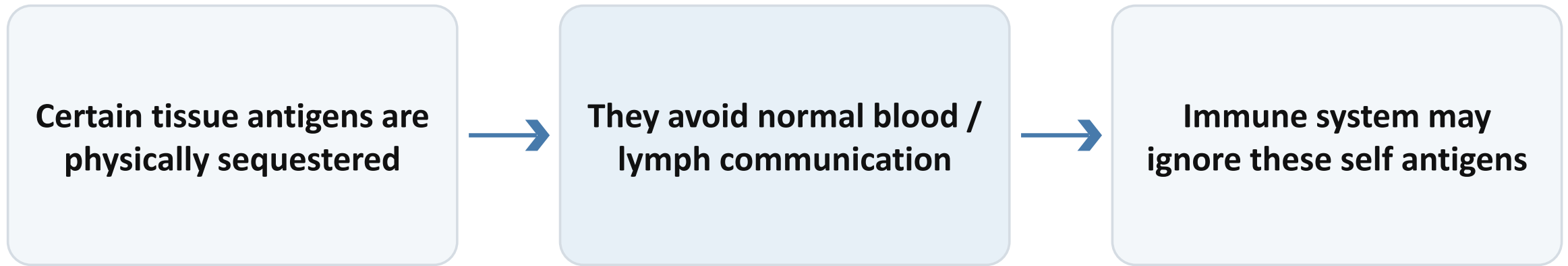
Deletion pathway is
compromised

Clinical phenotype

Autoimmune
lymphoproliferative
disorder resembling lupus

The source illustrates loss of peripheral death-receptor deletion through ALPS.

Antigen sequestration prevents encounter



The source describes immune ignorance through sequestration rather than active silencing.

Immune-privileged sites in the source

Testis

Example of an immune-privileged site

Eye

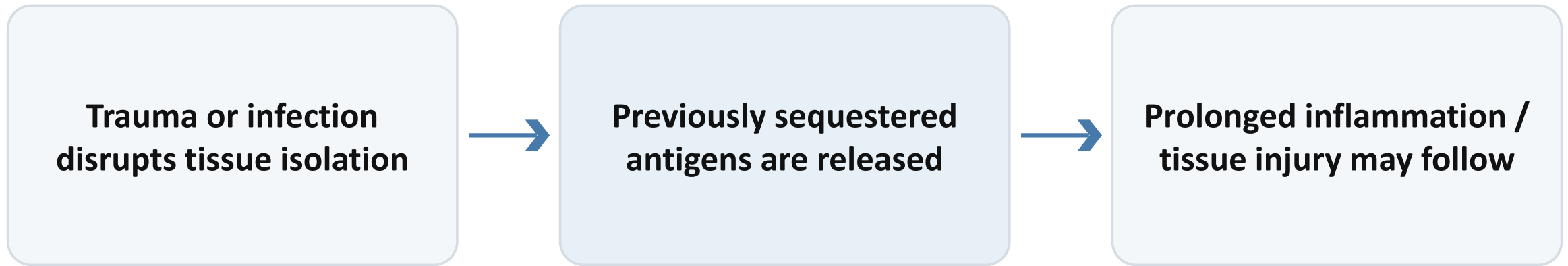
Example of an immune-privileged site

Brain

Example of an immune-privileged site

Testis, eye and brain are named as immune-privileged sites.

Injury can expose previously hidden self antigen



The text proposes exposure after injury as a cause of immune responses.

Posttraumatic orchitis is a proposed example

Testicular antigen release may trigger prolonged tissue inflammation

- The source presents this as a postulated mechanism.
- It is an example of loss of antigen sequestration.
- It should not be presented as universal for all orchitis.

Uveitis illustrates the same proposed principle

Ocular antigen exposure may provoke a damaging immune response

- Eye is listed as an immune-privileged site.
- Trauma or infection can reveal hidden antigens.
- This remains the source's proposed explanation, not a full uveitis taxonomy.

Silencing and sequestration are distinct

Anergy / suppression / deletion

- An immune cell has encountered antigen
- Response is impaired or cell removed

Sequestration

- Antigen may remain inaccessible
- Lack of antigen encounter limits response

Autoimmunity reflects failure of restraint



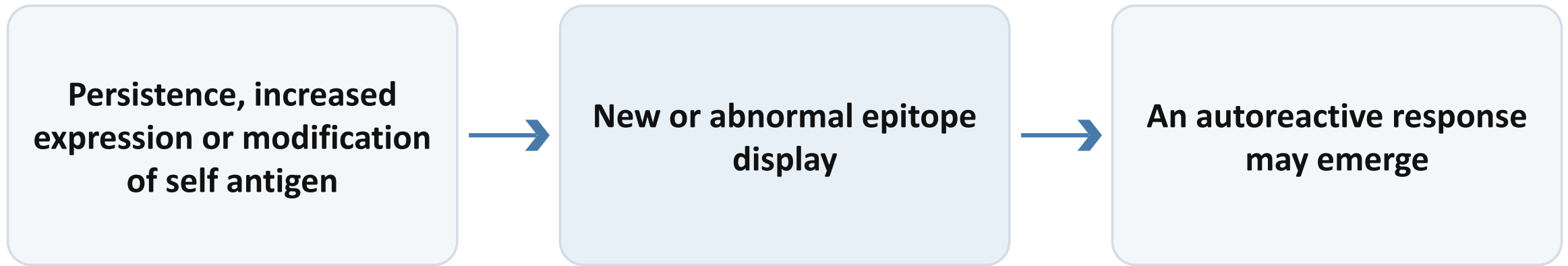
The adjacent general-principles section frames autoimmunity as failure of self-tolerance.

Susceptibility and environment both contribute



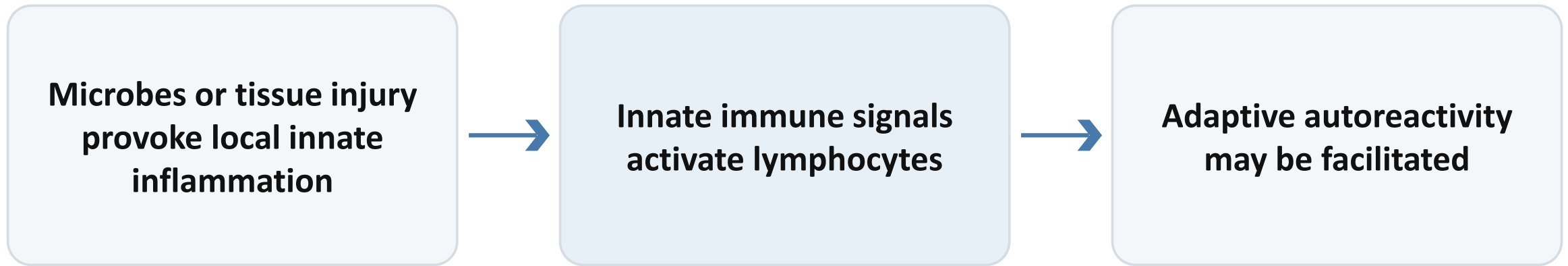
The source describes interactions between inherited risk and environmental stimuli.

Abnormal self-antigen display is another hypothesis



Altered display or neoepitopes are proposed contributors to autoimmunity.

Innate inflammation can initiate adaptive responses



Innate responses can serve as initiating conditions for adaptive responses.

Evidence strength varies among explanations

Strong illustrative mechanisms

- FOXP3 mutations → IPEX
- Fas/FasL mutations → ALPS
- CTLA4 variants → inflammatory disease

Less certain generalization

- Why tolerance fails in most common autoimmune disease
- Relative importance of altered antigen display or inflammation

Case: Antigen presented without costimulation

Hypothetical teaching vignette

A mature T cell recognizes a self peptide on a resting dendritic cell with weak B7 expression.

What is the likely functional fate of that T cell?

Reasoned answer

Anergy: Signal 1 without adequate CD28–B7 signal 2 does not fully activate the cell.

Case: Early multisystem autoimmunity with FOXP3 defect

Hypothetical teaching vignette

A hypothetical child with severe multisystem autoimmunity is found to have a pathogenic FOXP3 mutation.

Which peripheral safeguard is primarily impaired?

Reasoned answer

Treg-mediated suppression; The source identifies FOXP3-associated IPEX.

Case: Fas-pathway defect

Hypothetical teaching vignette

A hypothetical patient with autoimmune lymphoproliferation carries a pathogenic Fas-pathway mutation.

Which tolerance step is disrupted?

Reasoned answer

Death-receptor-mediated apoptotic deletion of self-reactive lymphocytes; ALPS is the linked syndrome.

Integrative map of peripheral tolerance

Prevent activation

Low costimulation / CTLA-4
/ PD-1

Suppress responses

FOXP3⁺ Tregs, IL-10, TGF- β

Remove or avoid antigen

Bim/Fas apoptosis;
Sequestration

Summary across all source mechanisms.

Mechanistic distinctions to retain

Safeguard	Primary proximal event	Principal outcome
Anergy	Self recognition without enough help	Functional unresponsiveness
Treg suppression	CTLA-4 and inhibitory cytokines	Inhibited immune response
Deletion	Intrinsic / extrinsic apoptosis	Loss of autoreactive clone
Sequestration	Antigen inaccessible	Immune ignorance

An editable synthesis of the four sources of peripheral tolerance.