

Role of Susceptibility Genes

Genetic architecture of autoimmune susceptibility

HLA associations · Immune regulation · Host–microbe defense

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain why common autoimmune diseases are generally multigenic rather than single-gene disorders.
- Interpret HLA association data without confusing susceptibility with disease causation.
- Connect non-HLA risk loci to lymphocyte signaling, self-tolerance, and microbial sensing.
- Distinguish common susceptibility variants from rare single-gene immune dysregulation.
- Integrate genetic background with environmental triggers in pathogenesis.

Autoimmune disease requires more than an allele

Inherited susceptibility

HLA and non-HLA variants

Immune regulation

Central and peripheral tolerance

Environmental context

Infection, inflammation or tissue injury

Pathologic expression

Self-reactive lymphocyte activation and tissue injury

The contributors interact; Inherited variation does not cause environmental exposure.

Most autoimmune disorders have complex genetic architecture

- Inherited susceptibility usually reflects multiple genetic loci acting together.
- Risk alleles may be present in healthy individuals; Clinical expression is not inevitable.
- Risk loci involve antigen presentation, lymphocyte control, and host responses to microbes.
- Common polygenic disease must be distinguished from rare monogenic immune dysregulation.

Twin studies support a genetic contribution

Evidence from twin studies

- Affected individuals' twins have higher autoimmune disease incidence than the general population.
- Concordance is greater in monozygotic than dizygotic twins.
- Shared inherited factors therefore contribute to susceptibility.

Limits of that evidence

- Twin concordance is not perfect.
- Non-genetic influences also matter.
- Concordance supports heritability—not a specific causal gene.

The direction of the twin findings here, not an exact concordance percentage.

Genetic association is not genetic destiny

A susceptibility allele increases disease odds; It does not establish that disease will occur.

The HLA-B27 example is especially instructive: Most carriers never develop ankylosing spondylitis.

Sources of genetic evidence

Twins and families

Heritable contribution to a phenotype

HLA associations

Alleles associated with immune-mediated disease

Genome-wide association

Common non-MHC susceptibility polymorphisms

Rare human mutations

Loss of individual regulatory pathways

Knockout mouse models

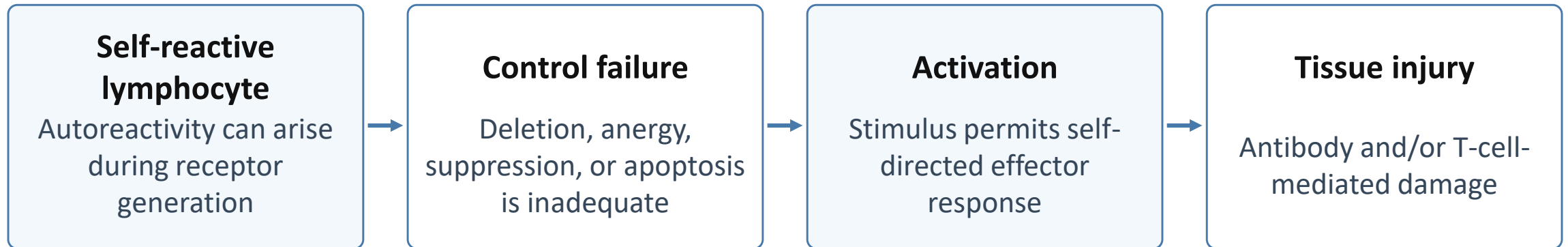
Experimental tests of immune control

Mechanistic studies

Potential pathway connecting variant and disease

An association, a mechanism, and a monogenic disease are different kinds of evidence.

How loss of self-tolerance produces autoimmunity



Risk genes can alter control points in this chain; Environmental stimuli can provide the activating context.

Central and peripheral tolerance target different stages

Central tolerance

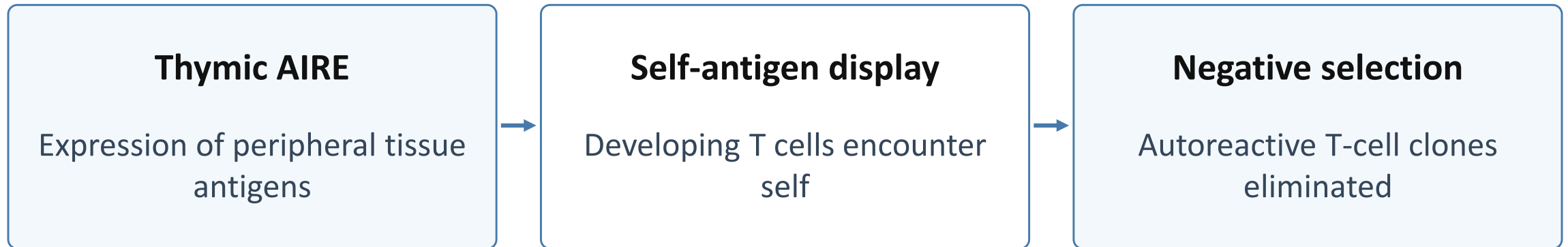
- Thymus for developing T cells; Bone marrow for developing B cells.
- Deletion of strongly autoreactive clones.
- B-cell receptor editing; Thymic regulatory T-cell development.

Peripheral tolerance

- Acts on mature lymphocytes after central selection.
- Anergy and inhibitory receptor signaling.
- Regulatory T-cell suppression and activation-induced apoptosis.

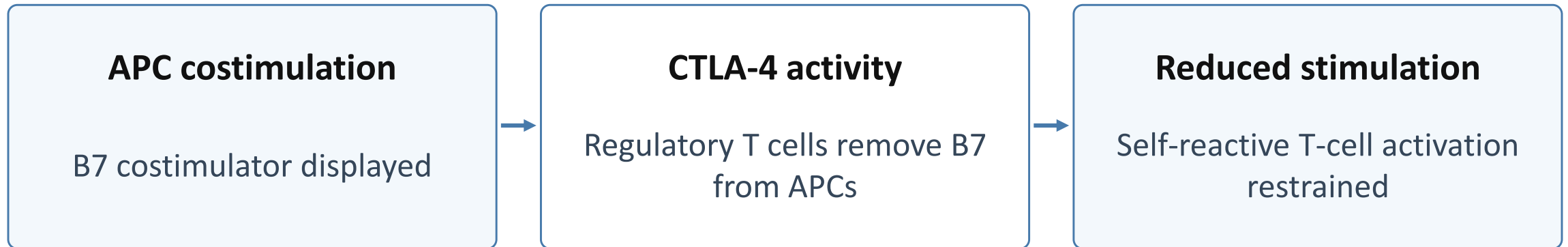
These are parent mechanisms required to understand why some susceptibility genes matter.

AIRE connects gene expression with central tolerance



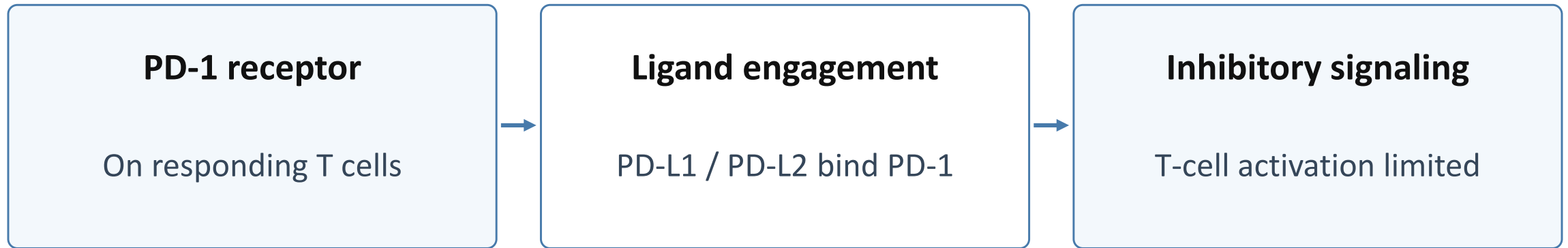
Loss-of-function AIRE mutations impair central tolerance and can cause autoimmune polyendocrine disease.

CTLA-4 restrains peripheral T-cell activation



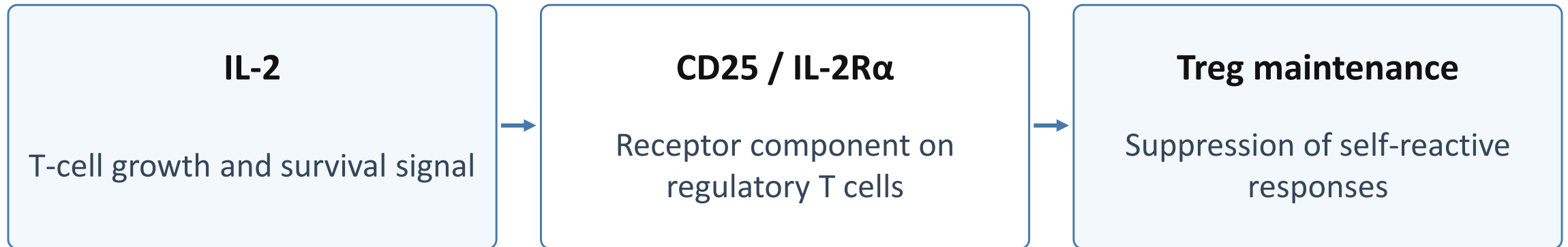
CTLA4 is both a disease-associated susceptibility gene and a rare monogenic checkpoint defect.

PD-1 provides another inhibitory signal



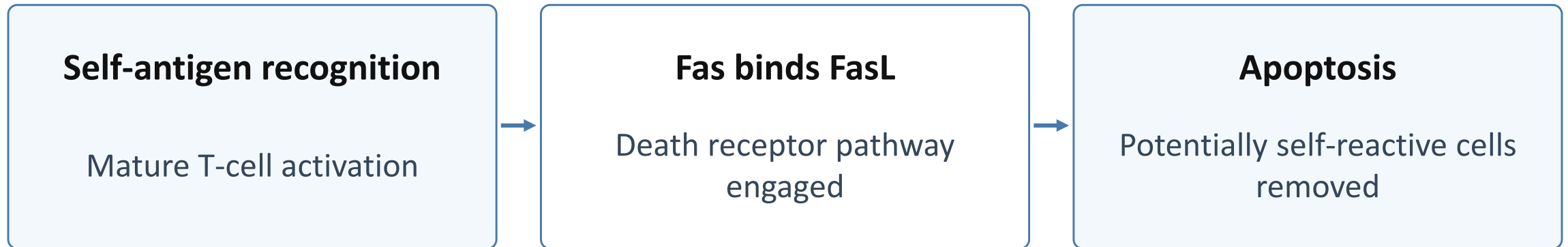
PD-1 deficiency as mechanistic evidence that immune inhibitory pathways prevent systemic inflammation.

IL-2 and CD25 sustain regulatory T-cell control



IL2RA polymorphisms may change the balance of regulatory and effector T-cell activity.

Fas–FasL signaling deletes activated autoreactive cells



Disruption of FAS or FASL can lead to autoimmune lymphoproliferative syndrome (ALPS).

Three categories of genetic involvement

HLA / MHC alleles

Variation in the antigen-presenting context

Non-HLA common variants

Variation in immune regulation and microbial defense

Rare single-gene disorders

Direct failure of a defined tolerance checkpoint

The first two account for much of common polygenic risk; The third demonstrates causal pathways.

HLA genes are major autoimmune susceptibility loci

- HLA associations are among the strongest genetic associations in autoimmune disease.
- Class I and class II alleles are associated with different disease phenotypes.
- Variation in peptide presentation is a plausible mechanism for several associations.
- The strength of an association differs across loci, diseases, and populations.

HLA class I and class II: Distinct contexts

Class I association

- HLA-B27 is the striking example in ankylosing spondylitis.
- Class I HLA associates with a major increase in disease odds.
- The allele is not sufficient to produce disease.

Class II association

- Multiple autoimmune diseases show class II HLA associations.
- HLA-DR and HLA-DQ alleles feature in the Robbins table.
- Certain molecules may preferentially present self or modified-self peptides.

Do not infer that all HLA associations act through the same proved molecular mechanism.

Antigen presentation links HLA with T-cell recognition

Self-peptide context

Natural or modified self peptide



HLA molecule displays peptide



Autoreactive T cell may respond

Disease context

Relevant HLA allele inherited



Tolerance / regulation is inadequate



Inflammatory activation occurs

Schematic causal possibilities; Individual allele–disease mechanisms vary in certainty.

The proposed HLA mechanism: Selective peptide display

- An HLA molecule binds and displays a subset of available peptides.
- Disease-associated alleles may preferentially present natural or modified self peptides.
- Certain such associations have mechanistic support, including in rheumatoid arthritis.
- Preferential peptide presentation is a disease-specific hypothesis—not a universal proof.

Association, mechanism, and causation are not synonyms

What an HLA association shows

- An allele occurs more frequently among people with a disease.
- The estimated odds differ between carrier and noncarrier groups.
- It supports inherited susceptibility.

What it does not establish

- That every carrier will develop disease.
- That the precise biologic pathway is known.
- That the allele is sufficient or always required.

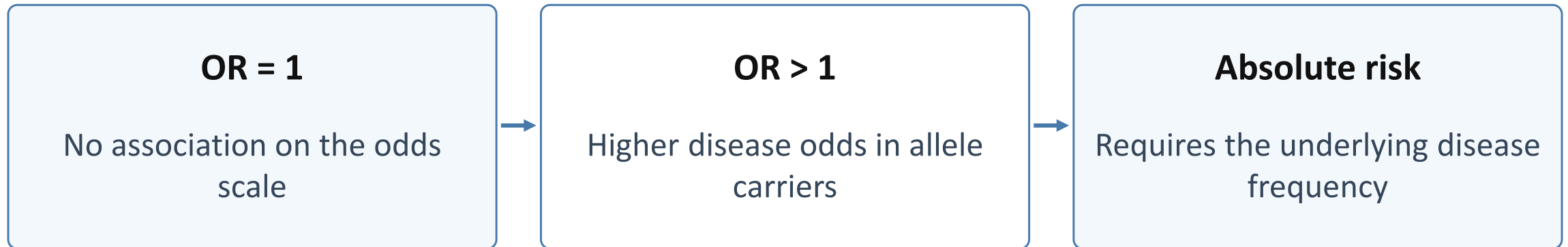
Risk alleles modify probabilities; Do not equate them with diagnostic criteria.

HLA-B27: An exceptional association

Ankylosing spondylitis is associated with HLA-B27 at an approximate odds ratio of 100–200.

This source estimate comes from populations of European ancestry and does not provide absolute risk.

How to read an odds ratio without overclaiming



A large odds ratio is not the proportion of carriers who will develop disease.

Clinical reasoning: HLA-B27 carrier

A healthy adult is incidentally found to carry HLA-B27. They have no history or findings suggestive of ankylosing spondylitis.

Reasoning prompt

- What does the carrier result establish about susceptibility?
- Can the allele alone establish ankylosing spondylitis?
- Why is a 100–200 odds ratio compatible with many healthy carriers?

Why most HLA-B27 carriers remain unaffected

- Carrying HLA-B27 is neither equivalent to having disease nor sufficient for disease development.
- Other inherited factors and environmental/immune contexts modify expression.
- The high odds ratio expresses a relative association, not a personal prognosis.
- A disease diagnosis requires evidence beyond a susceptibility genotype.

Rheumatoid arthritis: HLA-DRB1 shared epitope

The associated susceptibility alleles share a DRB1 sequence motif at positions 70–74.

Robbins Table 6.7 reports associations specifically for anti-CCP–positive rheumatoid arthritis.

Shared-epitope alleles in rheumatoid arthritis

One shared-epitope allele

- Table 6.7: Approximate odds ratio 4.
- DRB1 shared-epitope region: Amino acid positions 70–74.
- Estimate applies to anti-CCP–positive rheumatoid arthritis.

Two shared-epitope alleles

- Table 6.7: Approximate odds ratio 12.
- A stronger genotype association is shown.
- These are not direct estimates of penetrance.

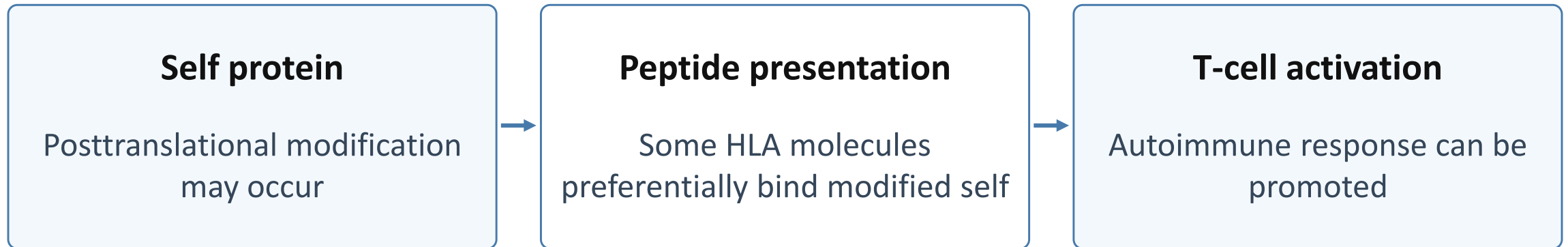
Anti-CCP denotes antibodies to cyclic citrullinated peptides.

HLA associations in anti-CCP–positive rheumatoid arthritis

Disease / phenotype	HLA genotype or haplotype	Approx. OR
RA, anti-CCP positive	DRB1: One shared-epitope allele	4
RA, anti-CCP positive	DRB1: Two shared-epitope alleles	12

Approximate odds ratios reported Table 6.7; European-derived populations.

Modified-self peptides can connect genotype to autoimmunity



This pathway is an explanatory possibility highlighted for rheumatoid arthritis; It is not inferred from an OR alone.

Type 1 diabetes: Class II HLA haplotypes

Disease / phenotype	HLA genotype or haplotype	Approx. OR
Type 1 diabetes	DRB1*0301–DQA1*0501–DQB1*0201	4
Type 1 diabetes	DRB1*0401–DQA1*0301–DQB1*0302	8
Type 1 diabetes	DRB1*0301/0401 heterozygotes	35

Distinct haplotype/genotype categories as reported; Not an individual absolute-risk calculator.

The type 1 diabetes example is genotype dependent

- Multiple HLA-DR/DQ haplotypes are associated with increased disease odds.
- The table lists a different association for the DRB1*0301/0401 heterozygous genotype.
- Genotype combinations cannot be reduced to the effect of one isolated allele.
- This does not mean that HLA genotyping alone diagnoses type 1 diabetes.

HLA associations: Multiple sclerosis and SLE

Disease / phenotype	HLA genotype or haplotype	Approx. OR
Multiple sclerosis	DRB1*1501	3
Systemic lupus erythematosus	DRB1*0301	2
Systemic lupus erythematosus	DRB1*1501	1.3

Approximate odds ratios; Small differences in the table should not be overinterpreted.

Celiac disease: HLA-DQ association

Disease / phenotype	HLA genotype or haplotype	Approx. OR
Celiac disease	DQA1*0501–DQB1*0201 haplotype	7

Presence of the susceptibility haplotype does not itself establish celiac disease.

Selected HLA–disease associations at a glance

Disease	Associated HLA category	Approx. OR
Ankylosing spondylitis	HLA-B27	100–200
Anti-CCP+ rheumatoid arthritis	DRB1: One / two shared epitopes	4 / 12
Type 1 diabetes	Listed DR/DQ combinations	4 / 8 / 35
Multiple sclerosis	DRB1*1501	3
Systemic lupus erythematosus	DRB1*0301 / *1501	2 / 1.3
Celiac disease	DQA1*0501–DQB1*0201	7

Source: Robbins Table 6.7; The odds ratios are approximate and population-specific.

Interpreting Table 6.7: Four essential cautions

- The reported odds ratios are approximate, not universal constants.
- Table values are drawn from European-derived populations.
- Association strength differs by phenotype definition; Rheumatoid arthritis is anti-CCP positive in the table.
- An odds ratio cannot be translated to absolute risk without baseline disease probability.

HLA allele vs haplotype vs genotype

Allele or motif

- HLA-B27 denotes a class I allele family.
- A DRB1 shared-epitope susceptibility motif spans positions 70–74.
- Alleles specify sequence-level variation.

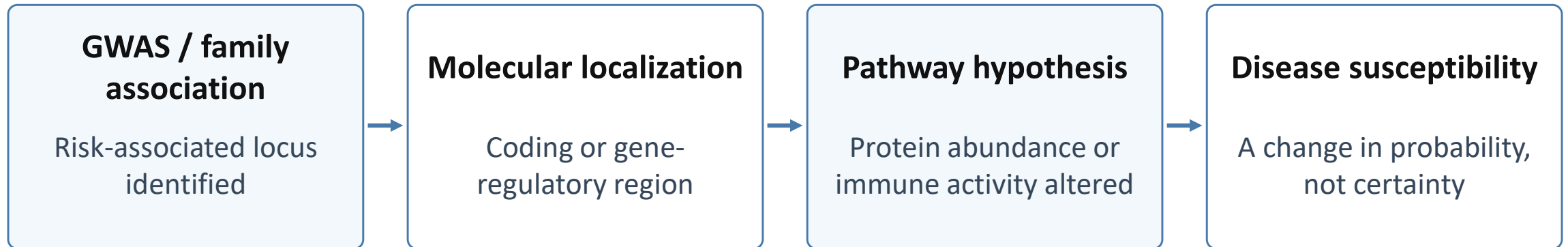
Haplotype or combination

- Certain DRB1–DQA1–DQB1 combinations are tabulated for type 1 diabetes.
- DRB1*0301/0401 heterozygotes form a distinct category.
- Do not apply an OR from one genetic category to another.

Common non-HLA polymorphisms modify disease susceptibility

- Family studies and genome-wide association studies reveal many non-MHC loci.
- Some loci are disease-associated; Others recur across multiple autoimmune disorders.
- The encoded proteins often regulate lymphocyte responses, tolerance, or microbial defense.
- A statistical association does not independently resolve variant function or causal direction.

From association signal to candidate mechanism



The source emphasizes that many implicated polymorphisms lie in regulatory DNA.

Noncoding regulatory variants vs coding variants

Regulatory polymorphism

- Often located in promoters or enhancers.
- May change the abundance, timing, or cellular location of gene expression.
- Most non-MHC associations discussed are of this broad type.

Protein-coding variant

- May change the sequence or function of an encoded protein.
- A plausible altered protein function still requires evidence.
- The source does not assign a molecular mechanism to every individual allele.

The regulatory-versus-coding distinction is a source-grounded generalization, not a claim about every locus.

The main non-HLA pathways in the source

Lymphocyte signaling

PTPN22

Regulatory T-cell maintenance

IL2RA / CD25; CTLA4

Th17 differentiation

IL23R

Microbial detection

NOD2

Autophagy / barrier integrity

ATG16L1

Type I interferon responses

IRF5 and IFIH1

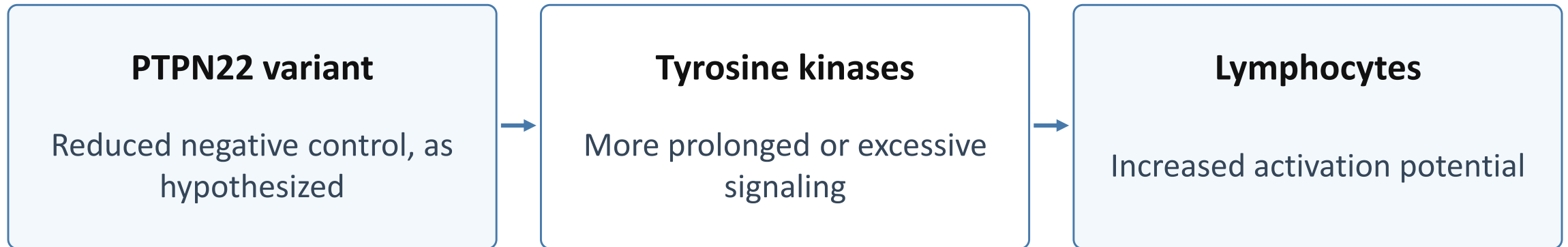
These are selected examples Table 6.8, not a comprehensive genetic atlas.

PTPN22 encodes a protein tyrosine phosphatase

The proposed function involves restraining lymphocyte tyrosine-kinase signaling.

Disease-associated variants are postulated to permit excessive lymphocyte activation.

PTPN22: A proposed route to lymphocyte hyperactivation

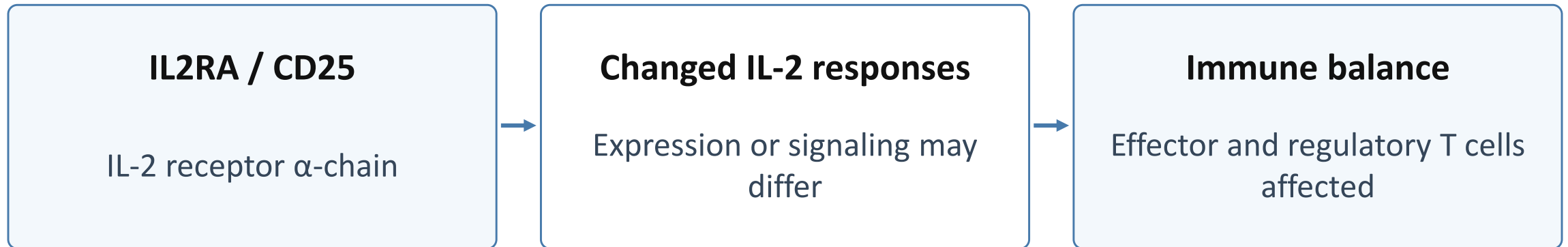


Robbins frames the mechanism as a postulate, not an experimentally settled mechanism for every allele.

PTPN22 has pleiotropic autoimmune associations

- Associations include rheumatoid arthritis and type 1 diabetes.
- Table 6.8 additionally includes inflammatory bowel disease.
- The same risk locus appears in phenotypically different disorders.
- This supports the concept of shared immune regulatory pathways.

IL2RA variants may alter the effector–Treg balance



Reported associations include type 1 diabetes and multiple sclerosis.

CD25 in disease association and immune tolerance

Normal biologic role

- CD25 is part of the IL-2 receptor.
- IL-2 is required to maintain functional regulatory T cells.
- Regulatory T cells restrain autoreactive lymphocytes.

Disease hypothesis

- IL2RA regulatory variants may alter receptor expression.
- A changed effector–regulatory balance can modify susceptibility.
- Specific consequences depend on the variant and context.

CTLA4: Common variation and rare defects

Common association

CTLA4 variants are associated with type 1 diabetes and RA

Normal checkpoint

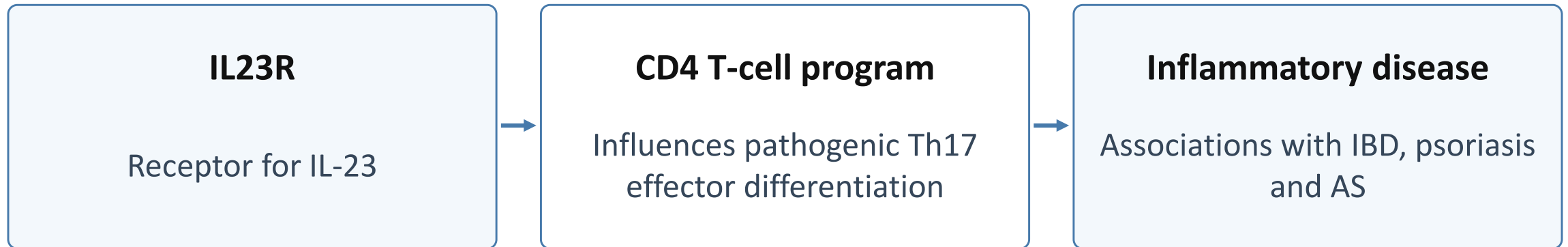
CTLA-4 restrains B7-mediated costimulation

Rare deficiency

Loss of checkpoint can cause systemic immune dysregulation

Independent lines of evidence support this pathway; Common alleles are not equivalent to knockouts.

IL23R connects susceptibility with Th17 differentiation

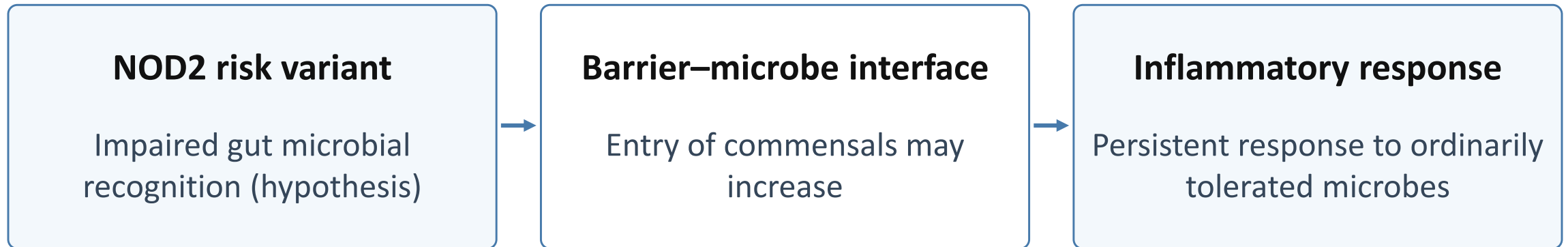


Robbins Table 6.8 proposes an effect on Th17 differentiation; Allele-specific functional changes are not detailed.

NOD2 senses microbes in the intestinal setting

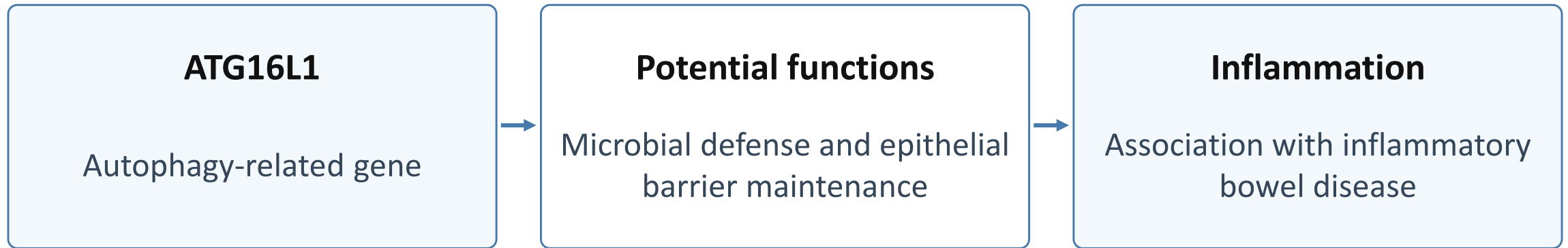
- NOD2 belongs to the intracellular NLR family of microbial sensors.
- It is expressed in intestinal epithelial cells, including Paneth cells, and other cells.
- NOD2 variants associate with Crohn disease, especially in some ethnic populations.
- This illustrates that susceptibility loci can affect barrier–microbe interactions.

NOD2: Proposed defect in commensal sensing



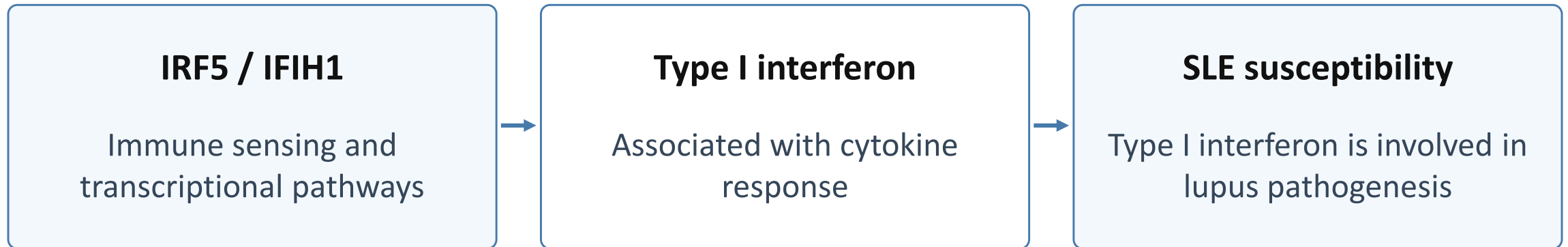
The proposed chain is not established for every NOD2-associated patient; Crohn disease is not simply a classic organ-specific autoantibody disorder.

ATG16L1 links autophagy to intestinal defense



The textbook table states a possible role; It does not establish a universal mechanism.

IRF5 and IFIH1 link susceptibility to type I interferon



A source-derived putative pathway; Gene-specific causal alleles are not specified in Table 6.8.

Non-HLA risk loci: Immune regulation

Gene	Associated diseases	Putative biologic role
PTPN22	RA; T1D; IBD	Lymphocyte signaling / negative control
IL23R	IBD; Psoriasis; AS	IL-23 signaling; Th17 differentiation
CTLA4	T1D; RA	T-cell inhibition / regulatory T-cell effects
IL2RA	MS; T1D	IL-2 signaling; Treg and effector balance

Associations and putative functions are derived Table 6.8.

Non-HLA risk loci: Response to microbes

Gene	Associated diseases	Proposed function
NOD2	IBD	Cytoplasmic bacterial sensor in gut epithelium
ATG16L1	IBD	Autophagy, microbial defense and epithelial barrier
IRF5; IFIH1	SLE	Type I interferon production / regulation

Inflammatory bowel disease encompasses more than conventional adaptive autoimmunity.

Two broad classes of non-HLA susceptibility loci

Immune response / tolerance

- PTPN22: Lymphocyte kinase signaling.
- CTLA4 and IL2RA: Inhibition and Treg homeostasis.
- IL23R: Effector T-cell differentiation.

Host–microbe / innate pathways

- NOD2: Intracellular microbial recognition.
- ATG16L1: Autophagy and intestinal barrier function.
- IRF5 and IFIH1: Type I interferon response.

Biological category is not an exclusive cell-type classification.

Rare single-gene disorders explain immune checkpoints

- Knockout experiments and inherited human mutations reveal specific tolerance pathways.
- AIRE, CTLA4, PD1, FAS, FASL, IL2, and CD25 among these checkpoints.
- Such mutations can produce severe immune dysregulation.
- They do not explain most common multigenic autoimmune diseases.

AIRE deficiency and polyendocrine autoimmunity

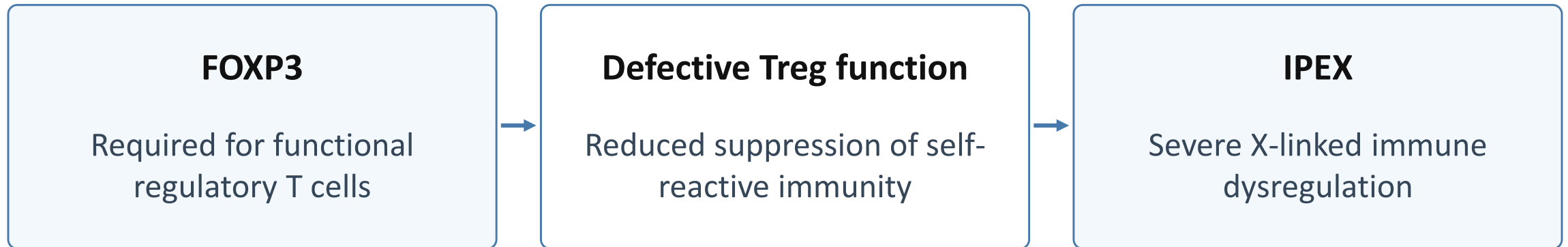
Normal AIRE-dependent step

- Expression of tissue-restricted self antigens within thymic selection.
- Self-reactive developing T cells can encounter those antigens.
- Negative selection removes some dangerous clones.

AIRE loss of function

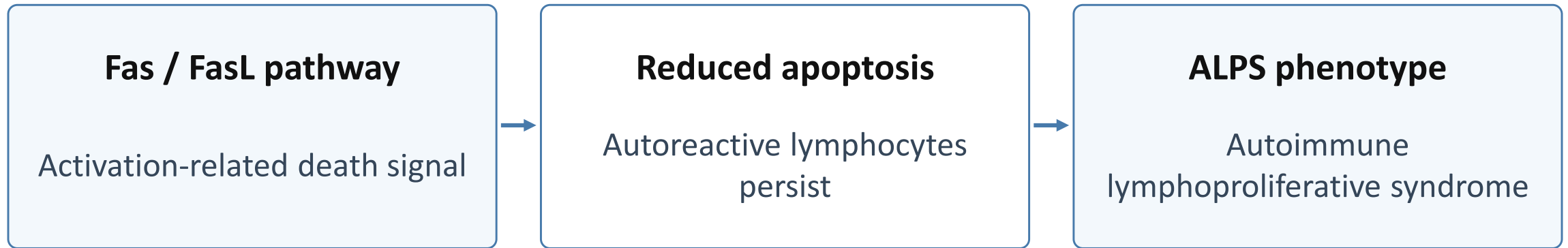
- Reduced central display of some self antigens.
- Impaired elimination of relevant autoreactive T cells.
- Rare autoimmune polyendocrine syndrome may result.

FOXP3 deficiency illustrates regulatory T-cell failure



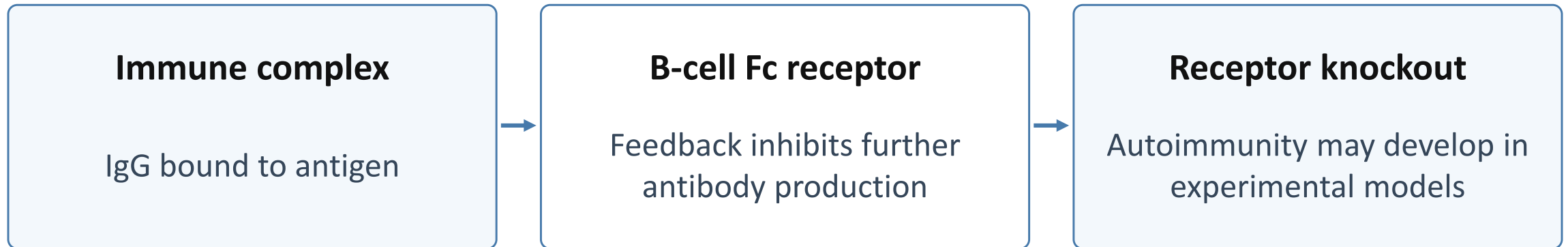
IPEX is an adjacent tolerance example, not a common risk polymorphism listed in Table 6.8.

FAS / FASL mutations impair lymphocyte deletion



A direct rare-pathway example rather than a common autoimmune susceptibility allele.

B-cell IgG Fc receptor supplies negative feedback



This pathway is cited in the subsection as experimental evidence of B-cell immune regulation.

Common susceptibility variants are not null mutations

Polygenic susceptibility

- Modest-to-large statistical associations are possible.
- Most carriers do not necessarily express disease.
- Often noncoding regulatory variants across many loci.

Rare monogenic dysregulation

- Defined genetic lesion can disrupt a critical immune pathway.
- Provides unusually direct evidence of checkpoint function.
- Not responsible for most common autoimmune conditions.

A common association is not evidence of a complete protein knockout.

Distinct genetic pathways in autoimmune susceptibility

Antigen presentation

HLA class I and class II

Central tolerance

AIRE-dependent thymic selection

Peripheral inhibition

CTLA4, PD-1 and Fas pathways

Effector signaling

PTPN22 and IL23R

Regulatory T cells

IL2RA / CD25 and FOXP3

Innate / barrier defense

NOD2, ATG16L1, IRF5 and IFIH1

These are parallel and interacting mechanisms, not a linear gene-to-gene signaling chain.

Case: Anti-CCP–positive rheumatoid arthritis

Two people with anti-CCP–positive rheumatoid arthritis have different DRB1 shared-epitope allele counts. The textbook table reports odds ratios of approximately 4 and 12 for the corresponding categories.

Reasoning prompt

- What type of association is being compared?
- Does the difference show that one patient must have more severe disease?
- Can these values alone predict the course of established arthritis?

Case: Crohn disease and NOD2 susceptibility

A study reports enrichment of a NOD2 polymorphism among people with Crohn disease in a particular ancestry group.

Reasoning prompt

- Which innate immune function is implicated by Robbins?
- What proposed mechanism might connect microbial recognition to intestinal inflammation?
- Which conclusions would require direct functional or clinical data?

Case: IL2RA association across diseases

An IL2RA regulatory-region polymorphism is associated with type 1 diabetes and multiple sclerosis in genetic studies.

Reasoning prompt

- What protein does IL2RA encode?
- Which cell population may be especially sensitive to disturbed IL-2 signaling?
- Why does a shared locus not imply identical disease pathogenesis?

Genetic finding: What can be concluded?

HLA-B27 detected

Increased susceptibility to AS;
Not a diagnosis

PTPN22 association

A plausible immune-regulatory
locus

Rare AIRE loss of function

Can disrupt thymic central
tolerance

IL2RA promoter variant

Potential altered IL-2
responsiveness

NOD2 risk polymorphism

Crohn association with
contextual mechanism

FAS disruption

Loss of an apoptotic tolerance
pathway

Genotype interpretation must match the strength and type of source evidence.

Five interpretation pitfalls to avoid

- Confusing odds ratios with an individual's probability of disease.
- Applying population-specific association estimates to all ancestry groups.
- Assuming that HLA carriage is sufficient for a clinical diagnosis.
- Treating postulated non-HLA mechanisms as established for every variant.
- Using rare knockout phenotypes as models of the magnitude of common-variant effects.

Susceptibility is expressed through gene–environment interplay

Inherited background

HLA and immune-regulatory variants

Environmental stimuli

Infection, tissue injury and inflammation

Tolerance control

Autoreactive lymphocytes may be restrained or activated

Disease expression

Only a subset of susceptible people develop tissue injury

Risk genes and exposures interact; Neither factor is an isolated sufficient cause.

Synthesis: What susceptibility genes teach us

- HLA associations highlight the importance of antigen presentation.
- Non-HLA polymorphisms identify immune regulatory, effector, and innate pathways.
- Rare monogenic disorders demonstrate why defined tolerance checkpoints matter.
- Disease expression remains probabilistic and depends on additional biologic context.

Core terminology for accurate genetic interpretation

Term	Meaning in this lecture
Susceptibility allele	Inherited variant associated with altered disease odds
Haplotype	Combination of linked alleles considered together
Shared epitope	Susceptibility-associated motif in HLA-DRB1 positions 70–74
GWAS	Genome-wide association study of genotype–phenotype patterns
Regulatory polymorphism	Variation potentially affecting gene expression
Monogenic immune defect	Rare mutation directly impairing a defined tolerance pathway

Definitions are intended for interpreting the Robbins evidence, not for genetic counseling.

Primary reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition · Elsevier · 2026.