

Defects in Adaptive Immunity

Primary immunodeficiencies of lymphocyte maturation, activation and immune regulation

T-cell arm

Cell-mediated immunity

B-cell arm

Antibody production

Regulatory arm

Tolerance and balance

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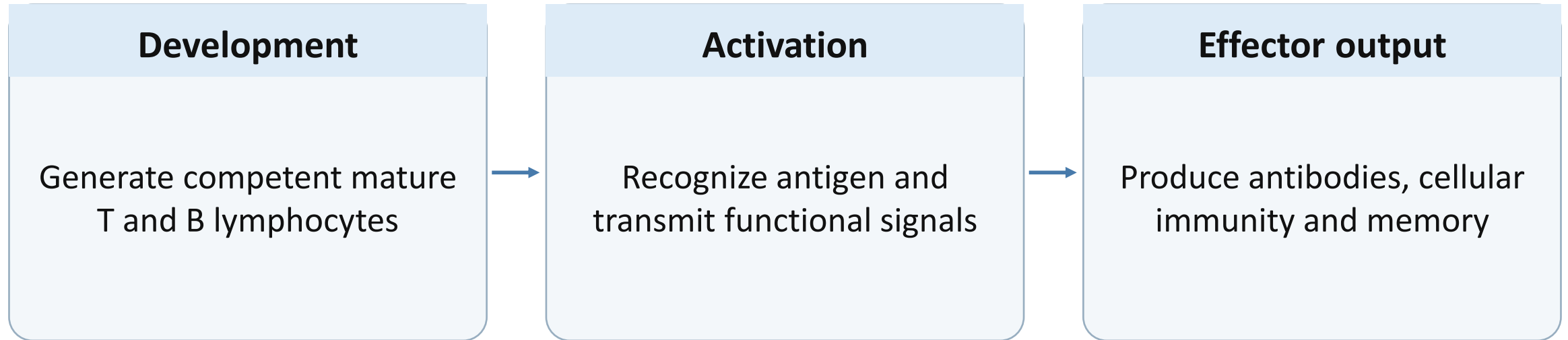
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Learning outcomes

- Distinguish defects of lymphocyte development from defects of immune activation and regulation.
- Explain genotype-to-phenotype links in the major adaptive immunodeficiencies.
- Predict infection patterns and lymphoid morphology from the affected immune compartment.
- Compare key disorders using immune-cell populations and immunoglobulin profiles.

Adaptive immunity requires three linked processes



The defect may arise at any step; Immune regulation overlays the process

T-cell and B-cell defects are not independent

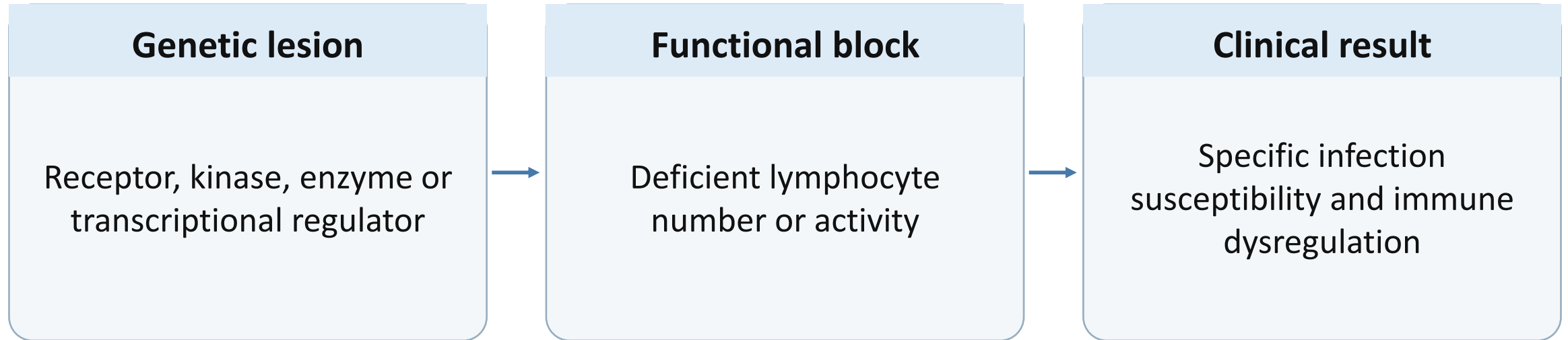
T-cell dysfunction

- Loss of cell-mediated microbial control
- Reduced helper signals to B lymphocytes
- Secondary impairment of antibody synthesis

B-cell dysfunction

- Poor immunoglobulin production
- Reduced antibody-mediated opsonization
- T-cell-mediated responses can be preserved

A molecular defect can produce a clinical immune phenotype



Classify disorders by primary functional bottleneck

Bottleneck	Source examples
Combined lymphocyte dysfunction	SCID; MHC class II deficiency
B-cell maturation	X-linked agammaglobulinemia
Thymic / T-cell development	DiGeorge syndrome
Helper signals and Ig diversification	Hyper-IgM syndrome
Late antibody differentiation	CVID; selective IgA deficiency
Cytotoxic control / regulation	X-linked lymphoproliferative disease; PIRDs

Microbial patterns reflect the defective immune task

- Broad bacterial, fungal and viral vulnerability suggests a combined defect such as SCID.
- Recurrent pyogenic respiratory infections point toward deficient antibody-mediated opsonization.
- Severe EBV infection is particularly characteristic of X-linked lymphoproliferative disease.
- Mucosal infections are a principal clue to deficient IgA-mediated defense.

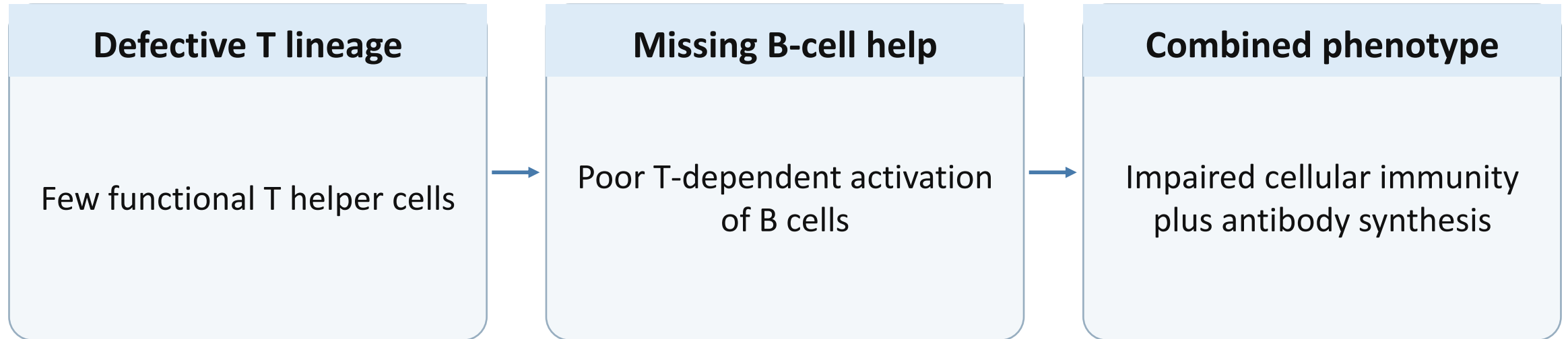
SCID is a shared phenotype, not one mutation

- Severe combined immunodeficiency (SCID) comprises genetically distinct disorders.
- Both humoral and cell-mediated responses are profoundly impaired.
- A primary T-cell abnormality may also prevent effective B-cell antibody production.
- Developmental failure occurs at different points in the lymphocyte lineage.

SCID presents early with widespread infection susceptibility

- Typical infant clues: Oral candidiasis, severe diaper dermatitis and failure to thrive.
- Infections can involve Candida, Pneumocystis, cytomegalovirus, varicella and pyogenic bacteria.
- Untreated disease is life-threatening in infancy; Hematopoietic stem-cell transplantation.

Why severe T-cell loss also causes antibody failure



Maternal T cells may cause neonatal GVHD in SCID

- Maternal lymphocytes can cross the placenta and persist in an immunodeficient infant.
- These transferred cells may attack host tissues and cause a morbilliform eruption.
- The rash reflects graft-versus-host disease, not a competent protective infant T-cell response.

X-linked SCID: Common γ -chain signaling failure

Common γ -chain defect

Shared signaling component
of several cytokine receptors



IL-7 response impaired

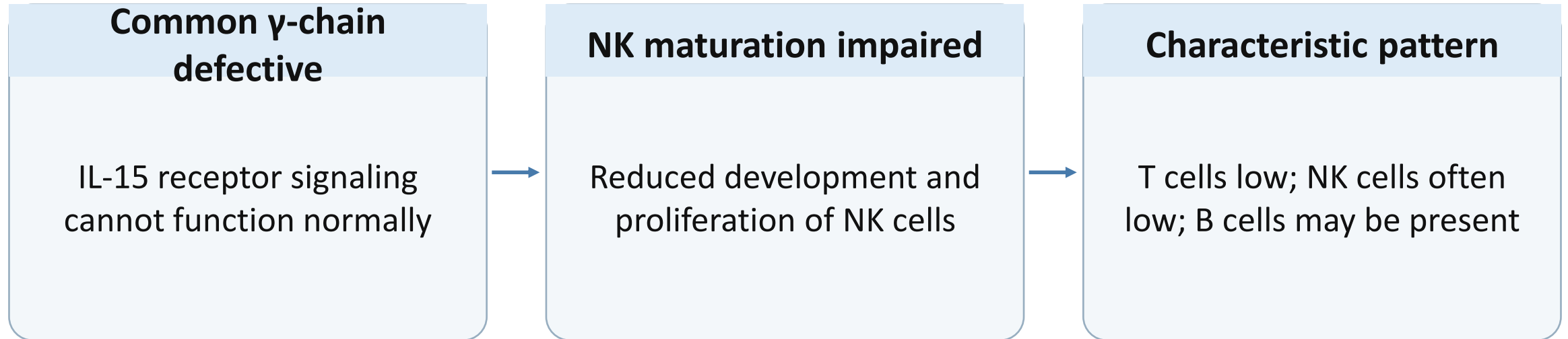
Poor survival and expansion
of developing T cells



T-cell deficiency

Severely reduced T cells;
Ineffective humoral response

The IL-15 pathway explains an NK-cell deficit



Lymphocyte number and function must be separated

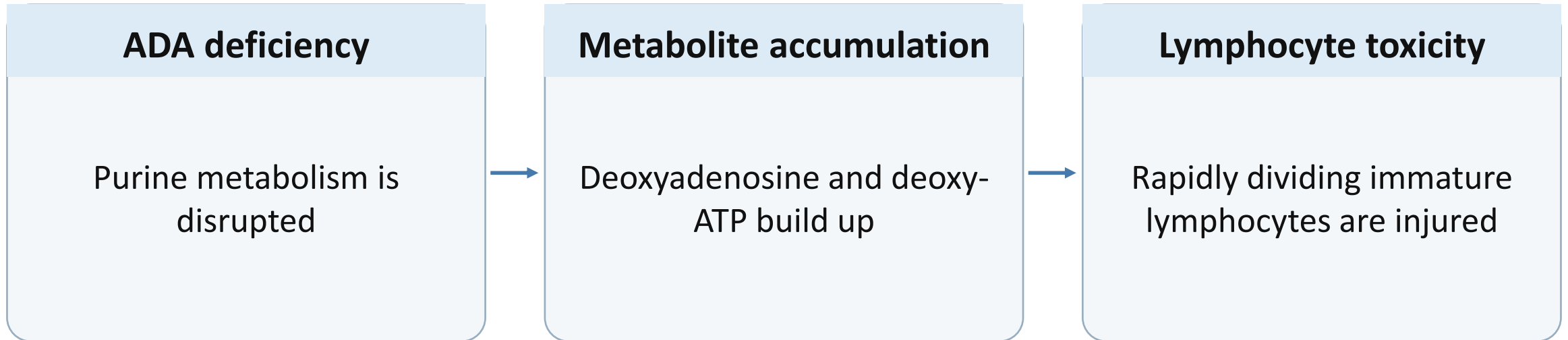
X-linked SCID: Cell numbers

- T cells markedly reduced
- B cells can be normal in number
- NK cells often deficient

X-linked SCID: Function

- Cell-mediated immunity severely reduced
- T-dependent antibody synthesis ineffective
- Recurrent infections across pathogen classes

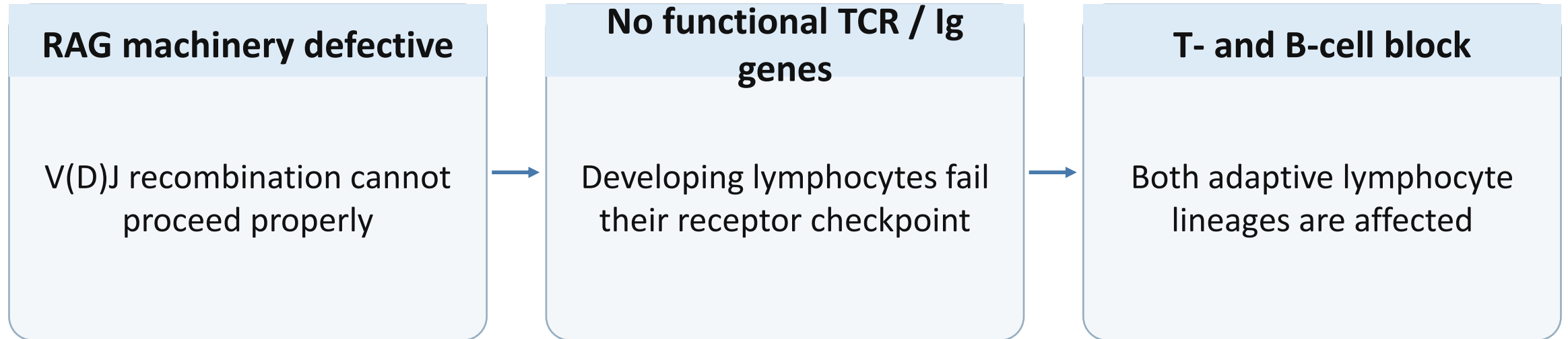
ADA deficiency: Toxic metabolites impair lymphopoiesis



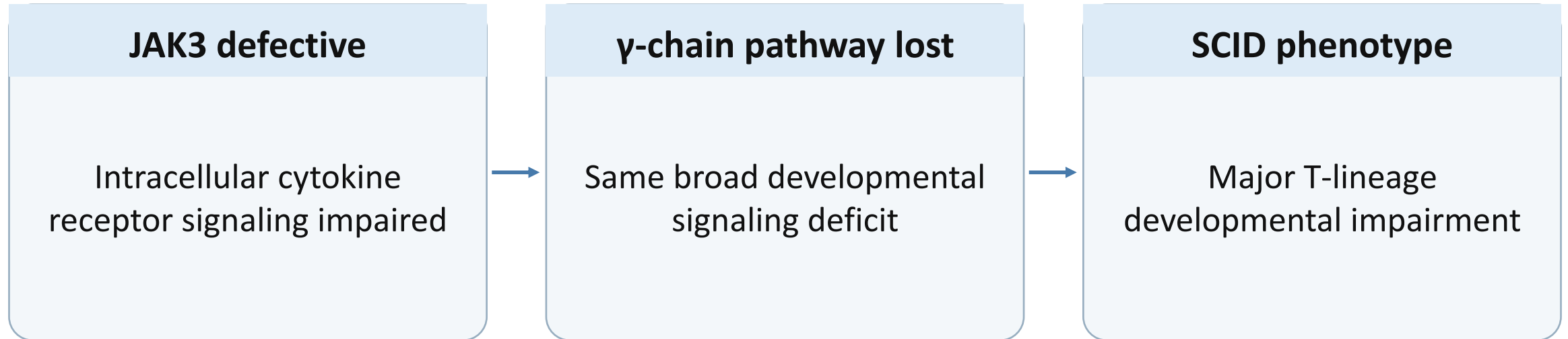
ADA-SCID often depletes T cells more than B cells

- The toxic metabolite model predicts marked injury to proliferating lymphoid precursors.
- T-lineage lymphocytes may be reduced more severely than B-lineage cells.
- The precise mechanistic contribution of accumulated metabolites is described as incompletely resolved.

RAG defects block assembly of antigen receptors



JAK3 mutation phenocopies common γ -chain failure



Additional SCID lesions impair T-cell receptor signaling

- Some disorders involve receptor chains, TCR-associated kinases or other signaling components.
- Abnormal calcium entry can also prevent normal lymphocyte activation.
- These mechanisms illustrate that profound immunodeficiency can arise after lymphocytes are initially generated.

SCID histology reflects failed lymphocyte maturation

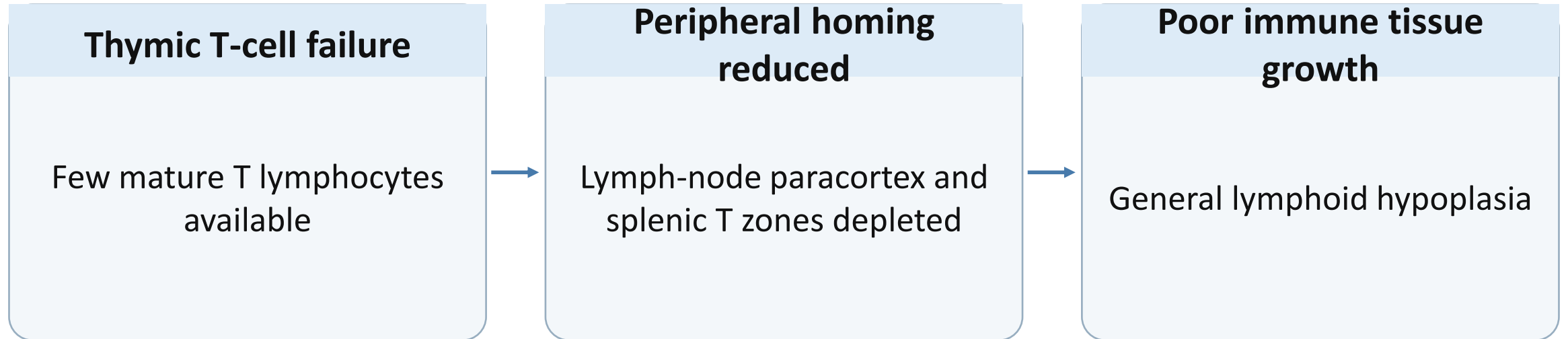
Thymus

- Small organ with marked lymphocyte depletion
- γ -chain disease may resemble fetal thymic epithelium
- ADA deficiency may retain Hassall corpuscle remnants

Peripheral lymphoid tissue

- Lymphoid organs are hypoplastic
- Marked depletion of T-cell regions
- Some forms also deplete B-cell compartments

Cell loss predicts the anatomy of lymphoid depletion



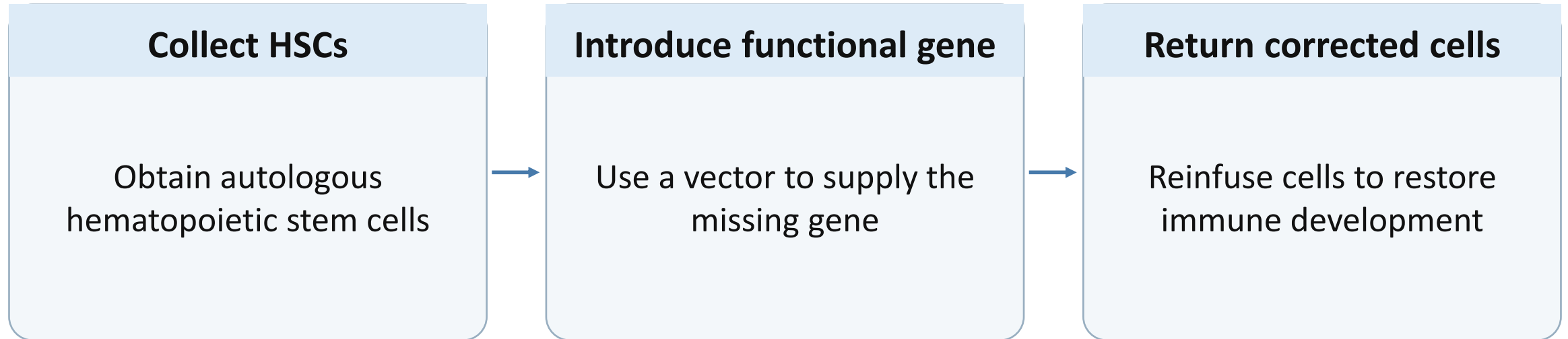
SCID: Four lesions, four mechanistic targets

Affected component	Primary mechanistic failure	Implication
Common γ -chain	Multiple cytokine receptor signals	T-cell development; often NK development
ADA	Purine metabolite clearance	Toxicity to developing lymphocytes
RAG proteins	Antigen receptor gene rearrangement	T and B receptor assembly
JAK3	Downstream cytokine-receptor signaling	γ -chain-like developmental phenotype

Stem-cell transplantation addresses the developmental block

- Hematopoietic stem-cell transplantation as the main SCID treatment.
- Donor-derived progenitors can generate functional immune lineages.
- The target is durable immune reconstitution, rather than treating each infection in isolation.

Ex vivo gene correction: Conceptual treatment sequence



Early SCID gene therapy exposed insertional oncogenesis

- Early viral-vector treatment of X-linked SCID achieved immune reconstitution in some patients.
- Integration near growth-control genes caused T-cell lymphoblastic leukemia in some early trials.
- The development of vectors designed to reduce this risk.
- These historical trial outcomes must not be treated as contemporary treatment-rate estimates.

ADA-SCID has multiple source-described replacement strategies

- Hematopoietic stem-cell transplantation replaces the affected lymphoid progenitors.
- Enzyme administration is described as another approach.
- Gene transfer into lymphoid precursors is also discussed.
- Specific protocols and current indications are outside the supplied source excerpt.

Clinical reasoning: A newborn with opportunistic infections

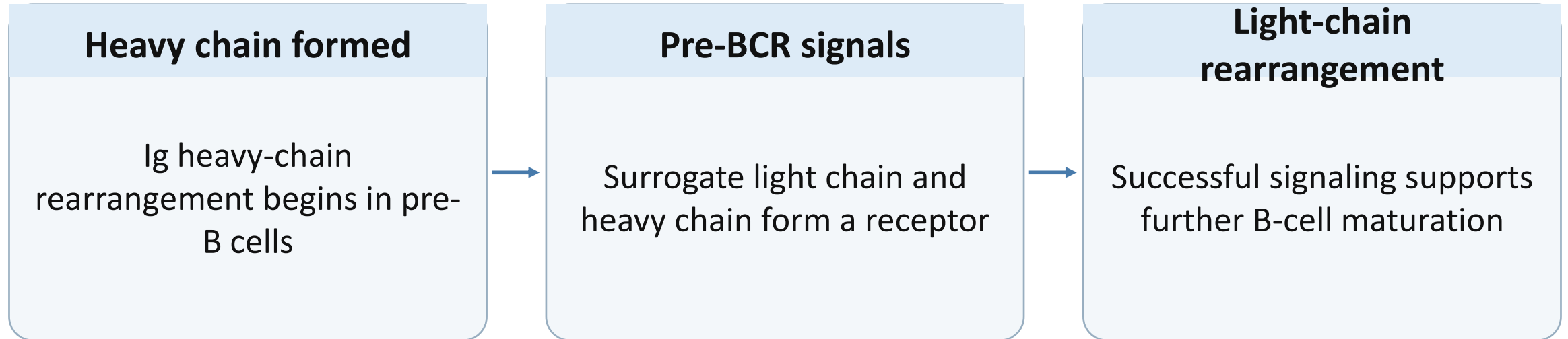
Illustrative vignette

An infant has persistent oral candidiasis, extensive diaper rash, failure to thrive and severe respiratory infection.

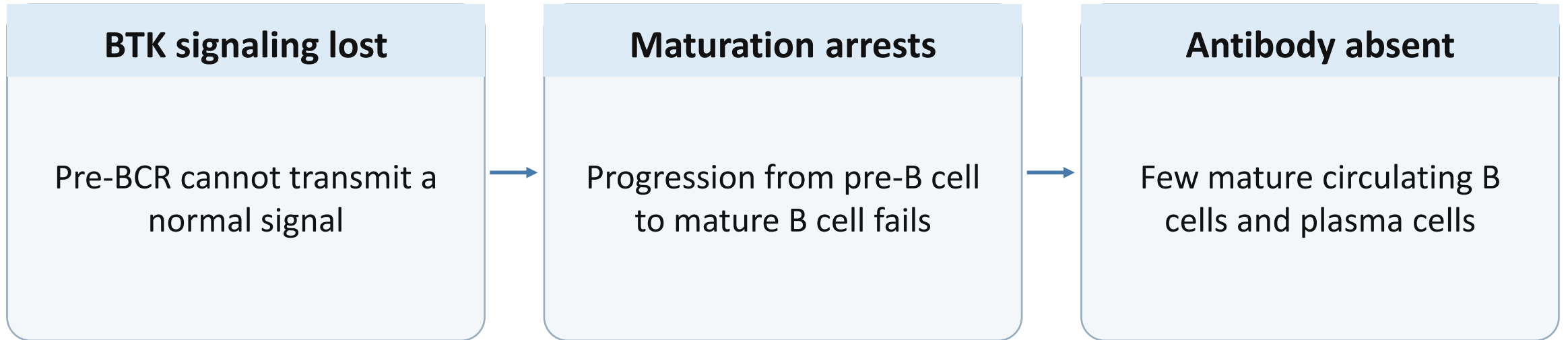
Which broad immune compartment is most likely defective?

Interpretation: A combined deficiency is more consistent with this spectrum than an isolated late-onset antibody defect.

Normal B-cell development uses the pre-BCR checkpoint



BTK mutation arrests B-cell maturation



Why X-linked agammaglobulinemia appears after infancy

- The disorder predominantly affects boys because the classic gene defect is X-linked.
- Maternal immunoglobulins offer temporary passive protection.
- Clinical infections commonly become apparent around 6 months as maternal antibodies wane.

Encapsulated and pyogenic bacteria expose absent antibodies

- Haemophilus influenzae, Streptococcus pneumoniae and Staphylococcus aureus are textbook examples.
- Recurrent otitis, sinusitis, bronchitis and pneumonia are common presentations.
- Poor antibody opsonization weakens phagocytic clearance of these organisms.

Enteroviruses are an important non-pyogenic exception

- Antibodies also neutralize some viruses before systemic dissemination.
- Echovirus, coxsackievirus and poliovirus vulnerability.
- Enteroviruses can spread from the gastrointestinal tract to the nervous system.
- Live poliovirus vaccination is specifically described as hazardous in this condition.

Giardia reflects loss of mucosal antibody defense

- Secreted IgA contributes to resistance against intestinal *Giardia lamblia*.
- Antibody deficiency can permit persistent protozoal infection.
- Preserved T-cell-mediated immunity still supports control of many fungal and intracellular infections.

X-linked agammaglobulinemia: Tissue and blood

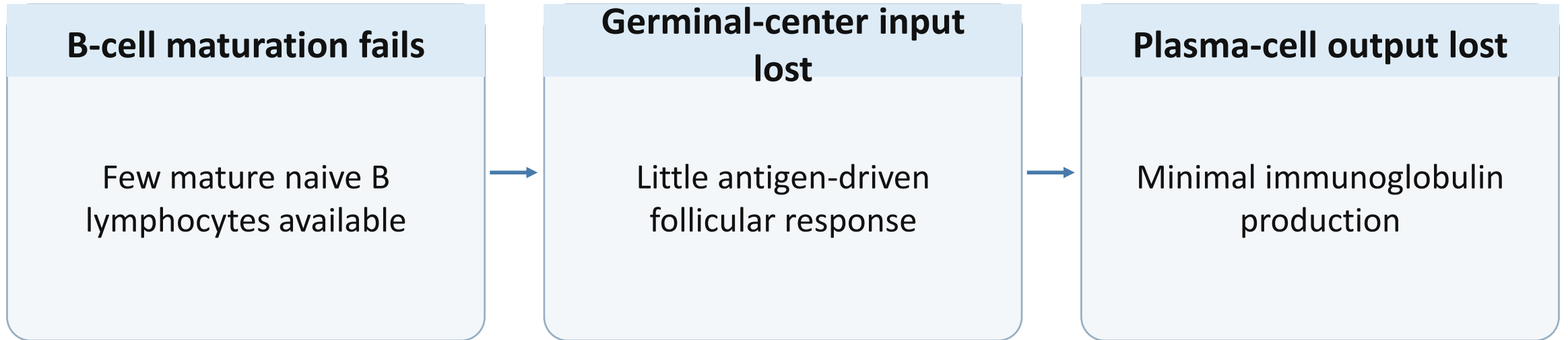
Circulating / marrow

- Mature blood B cells absent or markedly low
- All serum immunoglobulin classes reduced
- Pre-B lineage cells remain in marrow

Lymphoid tissue

- Germinal centers poorly developed
- Plasma cells are absent or markedly depleted
- T-cell responses remain functional

Why germinal centers and plasma cells are missing



Replacement immunoglobulin targets antibody function

- Immunoglobulin replacement is described as treatment for X-linked agammaglobulinemia.
- It compensates for deficient protective antibodies without correcting the BTK lesion.
- The source reports substantially improved survival with prophylactic IVIG.

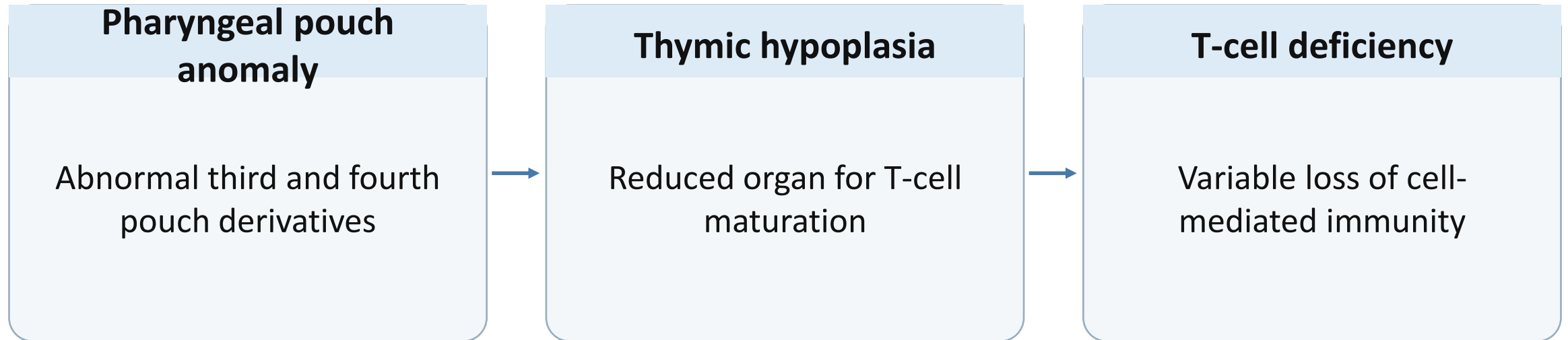
Autoimmune disease can coexist with profound antibody loss

- Arthritis and dermatomyositis are described despite severe hypogammaglobulinemia.
- The source suggests dysregulated self-tolerance or infection-driven inflammation as possibilities.
- The mechanism is not presented as definitively established.

Distinguish X-linked SCID from agammaglobulinemia

Feature	X-linked SCID	X-linked agammaglobulinemia
Main lesion	Common γ -chain	BTK
T lymphocytes	Greatly reduced	Preserved
B lymphocytes	May be present; poorly functional	Mature B cells markedly reduced
Signature risk	Broad opportunistic infections	Recurrent pyogenic / enteroviral infections

DiGeorge syndrome originates in embryologic development



Thymus and parathyroid defects cluster together

- Thymic hypoplasia or absence reduces T-cell maturation.
- Parathyroid developmental defects may produce hypocalcemic tetany.
- Congenital cardiovascular and craniofacial abnormalities may coexist.
- The combined phenotype is a developmental syndrome, not an isolated immune mutation.

22q11 deletion connects TBX1 to developmental anatomy

22q11 region affected

A germline deletion is described in most classic cases

TBX1 dosage altered

Branchial arch and great-vessel development disrupted

Multisystem phenotype

Thymic, parathyroid and cardiovascular features



DiGeorge: Immune phenotype versus tissue localization

Immune effect

- Low numbers of T lymphocytes
- Defective defense against some viral and fungal pathogens
- Ig concentration varies with helper function

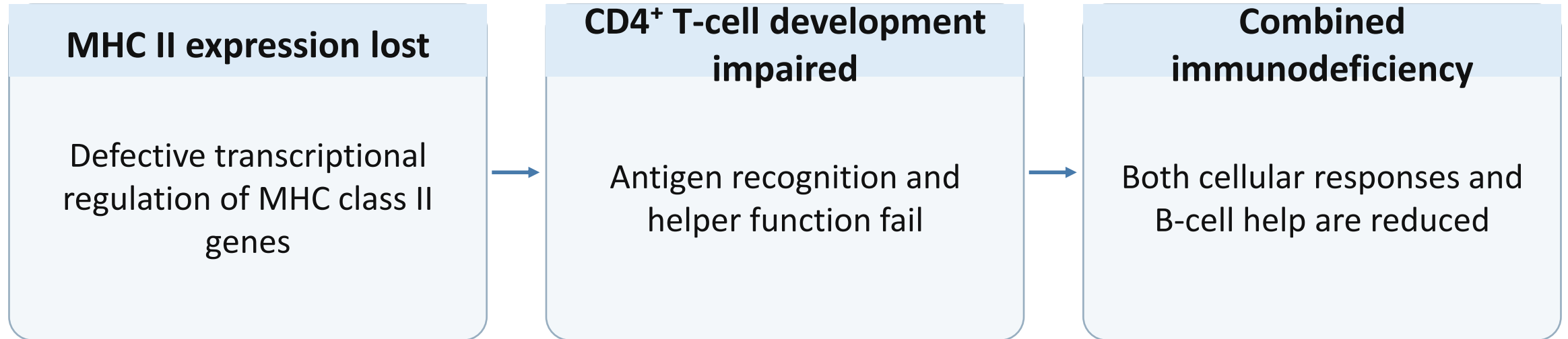
Morphologic correlate

- Thymus underdeveloped or absent
- Lymph-node paracortex depleted
- Splenic periarteriolar T-cell sheath depleted

DiGeorge T-cell deficiency varies in severity

- The thymic developmental defect can range from partial to profound.
- Immunoglobulin levels may be normal or depressed depending on T-cell support.
- Some improvement with age in patients who retain thymic tissue.

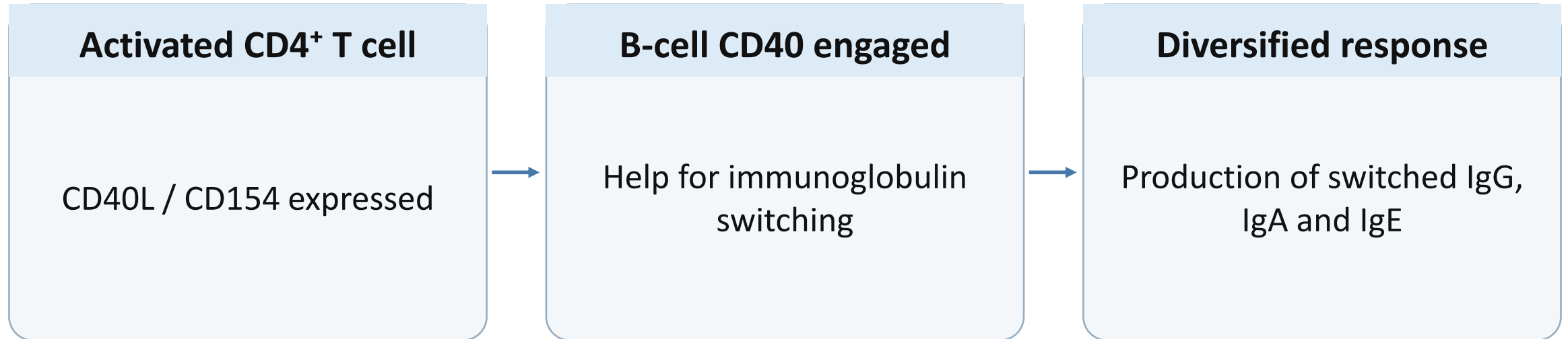
MHC class II deficiency blocks CD4⁺ T-cell development



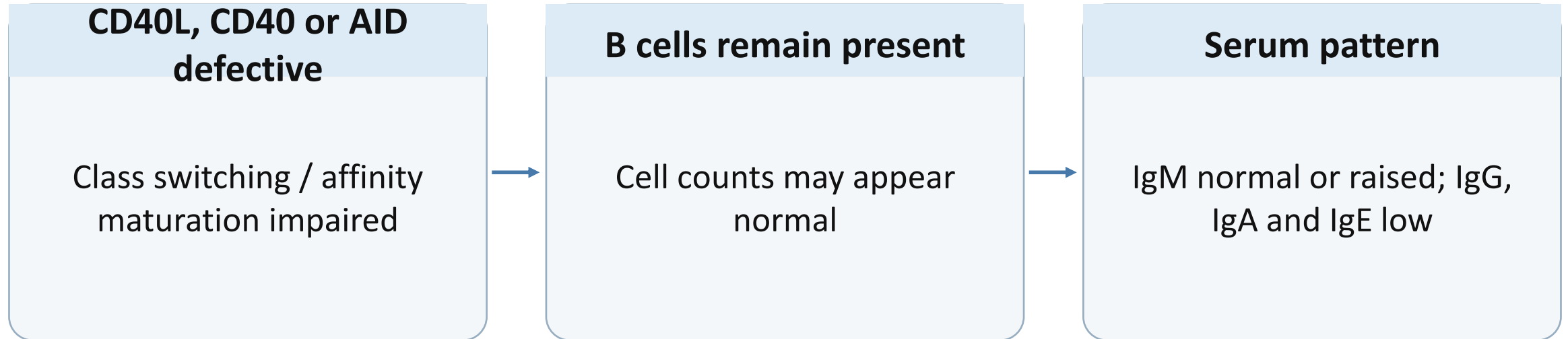
Developmental immune defects: Distinguishing clue

Disorder	Level of block	Teaching discriminator
DiGeorge syndrome	Thymic organ development	Multisystem congenital anomalies
MHC class II deficiency	MHC II expression	Deficient CD4 ⁺ T-cell maturation / activation
BTK deficiency	Pre-BCR signal	Very few mature B cells
RAG-associated SCID	Receptor rearrangement	Failure of both TCR and Ig assembly

Class-switch recombination requires helper T-cell signals



Hyper-IgM syndrome retains IgM but loses switched isotypes



Hyper-IgM: T-cell help failure or intrinsic B-cell defect

CD40L or CD40 defect

- Disrupts T–B interaction
- Ig class switching impaired
- Macrophage activation also reduced

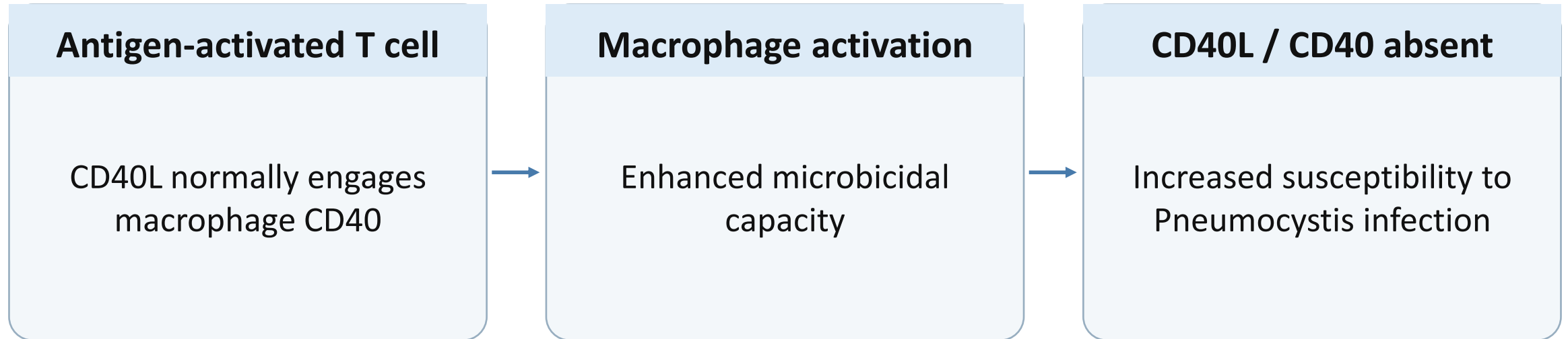
AID defect

- DNA-editing enzyme intrinsic to B cells
- Class switching and affinity maturation impaired
- Helper receptor interaction is not the primary lesion

Hyper-IgM infections reflect low high-affinity IgG

- Recurrent pyogenic infections result from deficient opsonizing IgG.
- Affinity maturation is also impaired, limiting high-affinity antibody generation.
- Normal peripheral B-cell numbers do not exclude this substantial functional defect.

CD40L–CD40 also activates macrophages



Hyper-IgM can have noninfectious manifestations

- IgM antibodies occasionally react with blood cells, causing autoimmune cytopenias.
- Described findings include hemolytic anemia, thrombocytopenia and neutropenia.
- Older patients may develop IgM-producing plasma-cell accumulations in gastrointestinal mucosa.

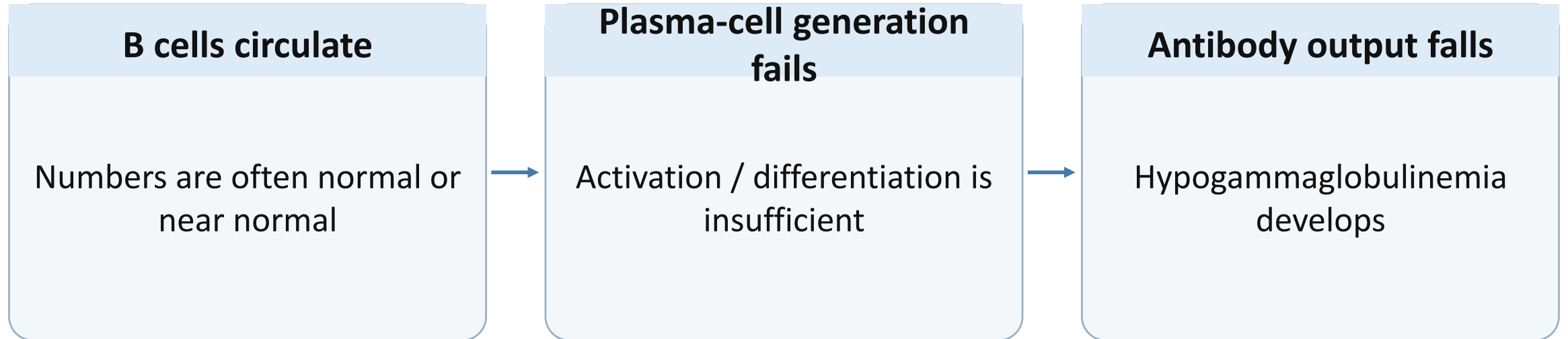
Ig profiles distinguish two antibody-production blocks

Feature	Agammaglobulinemia	Hyper-IgM syndrome
B-cell presence	Mature B cells few or absent	Mature B cells present
IgM	Low	Normal or elevated
IgG / IgA / IgE	Low	Very low / absent
Pathway	Early B-cell maturation	Class switch and affinity maturation

CVID is a heterogeneous hypogammaglobulinemic syndrome

- Common variable immunodeficiency (CVID) includes familial and sporadic presentations.
- Immunoglobulins are reduced across classes, although the pattern can preferentially involve IgG.
- The textbook frames the diagnosis around exclusion of defined alternative causes.
- No single molecular lesion defines all cases.

CVID: Mature B cells fail terminal differentiation



CVID illustrates both B-cell and helper-cell defects

B-cell survival / differentiation

- BAFF receptor-related defects are examples
- Plasma-cell differentiation may be impaired
- Pathways are genetically heterogeneous

T-cell help / Tfh regulation

- ICOS is an illustrative molecular defect
- ICOS participates in Tfh development
- Tfh-dependent B-cell activation may fail

CVID infections resemble other antibody deficiencies

- Recurrent sinopulmonary pyogenic infection is a hallmark.
- The source also describes herpesvirus recurrences and serious enterovirus disease.
- Persistent Giardia-associated diarrhea is another important manifestation.
- The typical onset is later than X-linked agammaglobulinemia.

CVID can have enlarged germinal centers but few plasma cells

B lymphocytes respond

Antigen-driven follicular proliferation persists



Germinal centers enlarge

Hyperplastic follicular architecture appears



Terminal differentiation fails

Plasma-cell formation remains inadequate

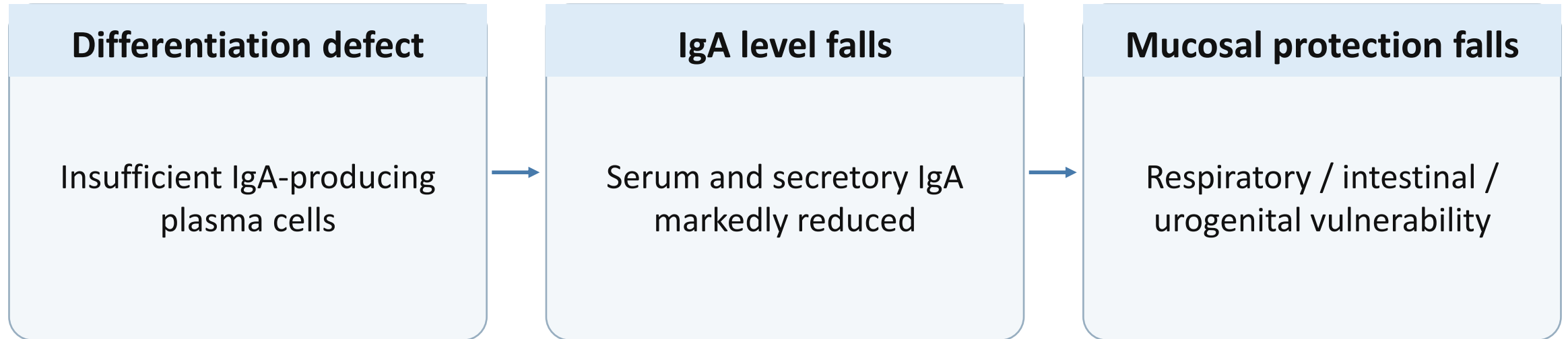
CVID includes autoimmunity and malignancy risk

- Autoimmune disease is an established association; Rheumatoid arthritis is a textbook example.
- Lymphoid malignancies occur more frequently in affected individuals.
- The source also reports an increased occurrence of gastric cancer.
- Immune dysregulation therefore extends beyond recurrent infection.

BTK deficiency versus CVID: Tissue-level distinction

Feature	X-linked agammaglobulinemia	CVID
Age pattern	Often evident after maternal Ig wanes	Usually later in childhood / adolescence
Blood B cells	Markedly reduced	Often retained
Germinal centers	Underdeveloped	May be hyperplastic
Plasma cells	Absent	Insufficiently generated

Selective IgA deficiency weakens mucosal surveillance



IgA deficiency has a broad clinical spectrum

- Many affected individuals have no symptoms.
- Symptomatic individuals may have recurrent sinopulmonary infection or diarrhea.
- Respiratory allergy and autoimmune disorders are more frequent in this group.
- The molecular basis remains unexplained in many patients.

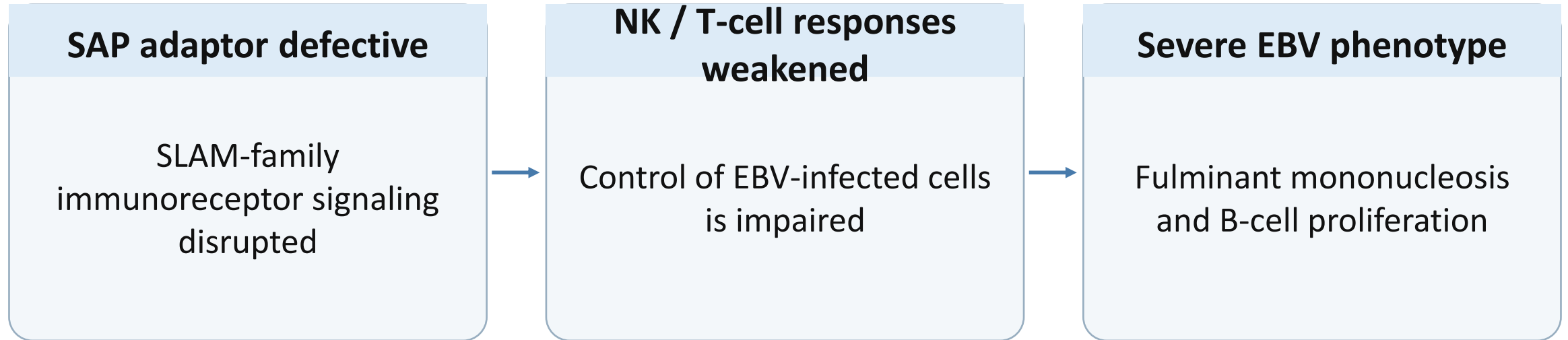
Transfusion reactions are a clinically relevant IgA caveat

- Some IgA-deficient patients can react severely when exposed to donor IgA.
- The possibility of life-threatening anaphylaxis.
- This is a risk in a subset of patients, not an inevitable outcome of IgA deficiency.

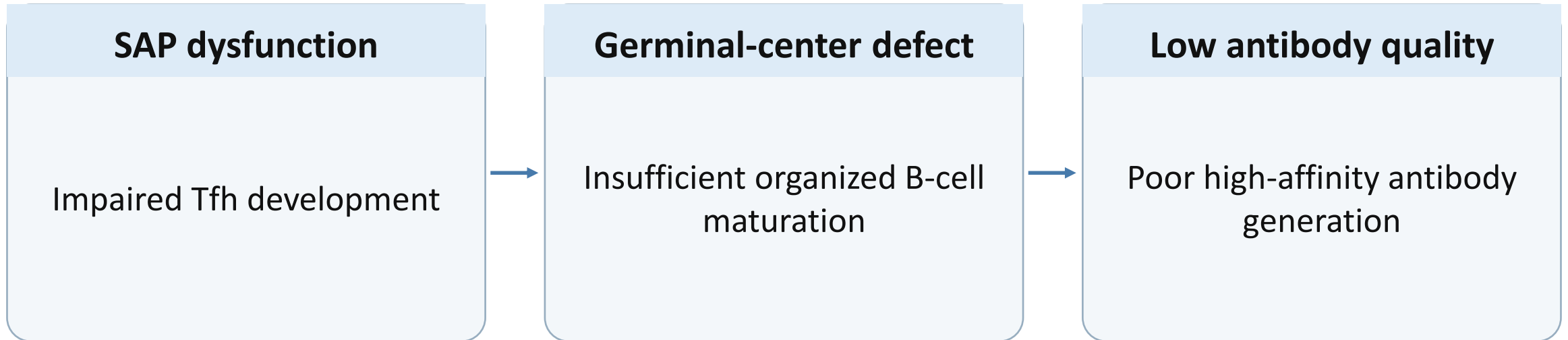
Antibody syndromes: Dominant defect at a glance

Disorder	Primary abnormality	Typical clue
X-linked agammaglobulinemia	Mature B-cell deficiency	Early pyogenic infections
Hyper-IgM syndrome	Immunoglobulin class-switch failure	IgM retained; switched isotypes deficient
CVID	Plasma-cell differentiation / help	Low Ig; B cells often present
Selective IgA deficiency	IgA secretion impaired	Asymptomatic or mucosal infection

XLP impairs cellular control of EBV-infected B cells



SAP also supports T follicular helper cell development



XLP is unusually selective for severe EBV disease

- The source emphasizes extreme susceptibility to Epstein–Barr virus.
- Fulminant infectious mononucleosis and B-cell tumors are characteristic outcomes.
- The reason for relative selectivity compared with other viral infections is uncertain.

Other activation defects can impair Th17 defense

- Lymphocyte activation requires intact receptor-associated biochemical pathways.
- Impaired Th17 responses are associated in the source with mucocutaneous candidiasis.
- The textbook also describes bacterial skin infections in the associated clinical phenotype.

Primary immune regulatory disorders cause dysregulated immunity

- PIRDs arise when molecular circuits that restrain or coordinate immune responses fail.
- The resulting phenotype can combine autoimmunity, infections and lymphoproliferation.
- Some syndromes also carry a malignancy risk.
- Immune activation can be excessive even when host defense is ineffective.

Gain-of-function signaling can amplify cytokine responses

STAT1 / STAT3 / JAK1 GOF

The source gives these as
PIRD examples

Signaling tone increased

Cytokine downstream
activity amplified

Immune dysregulation

Autoimmune / infectious
manifestations coexist



CTLA-4 insufficiency weakens inhibitory signaling

CTLA-4 dosage reduced

A negative regulatory checkpoint is weakened



Activation threshold shifts

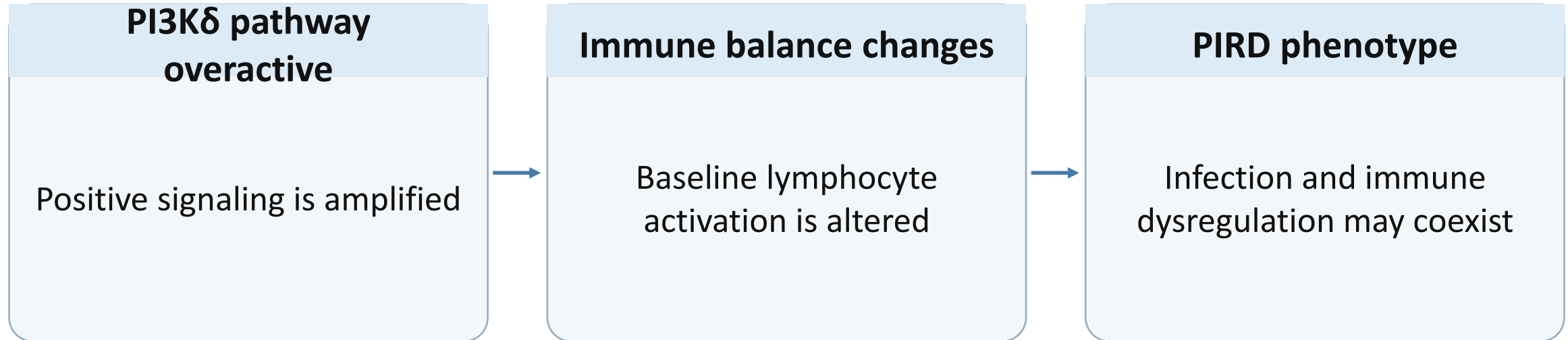
Normal immune inhibition is insufficient



Dysregulated responses

Early autoimmunity and lymphoproliferation may emerge

Activated PI3K δ syndrome increases pro-activation signals



Regulatory T-cell defects damage immune tolerance



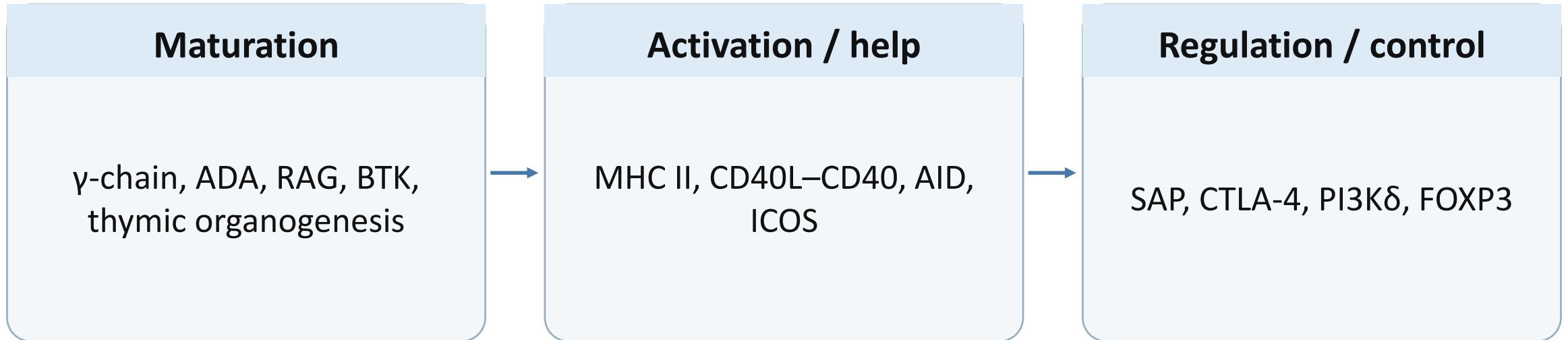
PIRD mechanisms share a dysregulation endpoint

Mechanism	Source examples	Principal functional change
Excess cytokine signal	STAT1, STAT3, JAK1 GOF	Hyperactive signaling
Reduced inhibitory checkpoint	CTLA-4 haploinsufficiency	Insufficient restraint
Amplified activation	Activated PI3K δ syndrome	Increased positive signaling
Failed regulatory tolerance	FOXP3, STAT5B deficiencies	Impaired Treg control

Targeted therapy is pathway-dependent in PIRDs

- JAK inhibitors as an example in certain STAT gain-of-function syndromes.
- Such pathway-directed treatments do not generalize to every PIRD.
- The excerpt does not provide gene-specific treatment algorithms or outcomes.
- Management details beyond these statements require separate guideline review.

One pathway map connects major adaptive deficiencies



Immune readouts guide differential diagnosis

Typical finding	Most informative diagnostic direction
T cells profoundly reduced + opportunistic infections	SCID / severe T-cell development defect
Mature B cells profoundly reduced + low all Ig	BTK-related agammaglobulinemia
Normal B counts + IgM retained / switched Ig low	Hyper-IgM syndrome
B counts often normal + broad hypogammaglobulinemia	CVID
Marked IgA reduction + mucosal infections	Selective IgA deficiency

Clinical reasoning: Repeated pyogenic respiratory infections

Illustrative vignette

A male infant develops otitis, sinusitis and pneumonia after the first months of life;
Mature blood B cells are nearly absent.

Which maturation checkpoint best explains this pattern?

Interpretation: BTK-dependent pre-B receptor signaling is defective in classic X-linked agammaglobulinemia.

Clinical reasoning: IgM is retained but IgG is very low

Illustrative vignette

A child has recurrent pyogenic infection with circulating B cells and normal-to-raised IgM, but marked loss of switched immunoglobulins.

Which immune interaction or enzyme should be evaluated?

Interpretation: Consider class-switch pathway defects involving CD40L, CD40 or AID.

Clinical reasoning: Severe EBV infection

Illustrative vignette

A boy develops unusually severe infectious mononucleosis and B-cell lymphoproliferation after EBV infection.

Which adaptive immune signaling disorder is characteristic?

Interpretation: SAP-related X-linked lymphoproliferative disease impairs NK/T-cell antiviral control.

Clinical clues separate immune deficiency from dysregulation

Deficient effector capacity

- Severe or recurrent pathogen-specific infections
- Low mature lymphocyte numbers or antibody output
- Tissue hypoplasia may parallel absent lineage

Dysregulated activation / tolerance

- Early autoimmunity and lymphoproliferation
- Mutations alter activation or inhibitory balance
- Infection susceptibility may coexist

Core diagnostic logic from the chapter

- First identify the failing compartment: T cells, mature B cells, secreted antibody or regulation.
- Then localize the failed checkpoint: Development, antigen-receptor signaling, T-cell help or tolerance.
- Interpret infections and lymphoid morphology together; Neither alone specifies the genotype.
- The source provides mechanistic syndromes, not a complete modern laboratory-testing algorithm.

Summary: Developmental blocks versus late functional defects

- SCID, DiGeorge syndrome and BTK deficiency primarily disrupt immune-cell development.
- Hyper-IgM syndrome and CVID chiefly impair effective antibody diversification or differentiation.
- SAP defects threaten EBV control; PIRDS disturb activation and tolerance.
- Clinical phenotype follows which defensive task has been lost or misregulated.

Primary source

Robbins, Cotran & Kumar

Pathologic Basis of Disease

11th edition (2026)

Chapter section: Defects in Adaptive Immunity