

Marginal Zone Lymphomas

Mature B-cell neoplasms arising in nodal, splenic, and extranodal tissues

Pathogenesis · Gastric MALT lymphoma · Diagnostic morphology · Clinical correlation

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Learning objectives

- Define the anatomic groups of marginal zone lymphomas (MZLs).
- Explain chronic antigen stimulation and the transition to autonomy.
- Connect BCL10–MALT1–NF- κ B signaling to lymphoma survival.
- Recognize gastric MALT lymphoma morphology and diagnostic evidence.
- Apply the pathology to treatment response and transformation risk.

Marginal zone lymphoma: Core definition

- A heterogeneous family of mature B-cell tumors.
- May arise in lymph nodes, the spleen, or extranodal tissues.
- Many cases derive from antigen-experienced memory B cells.
- Clinical behavior is often indolent, particularly at extranodal sites.

The anatomic site is a central organizing feature.

Anatomic classification of MZLs

Nodal

Presentation centered in lymph nodes; A member of the MZL family.

Splenic

Presentation centered in the spleen; Shares the MZL umbrella designation.

Extranodal / MALT

Involves mucosal or nonmucosal sites; Often arises with persistent inflammation.

The inflammation-dependent mechanism is most clearly established for extranodal MZL.

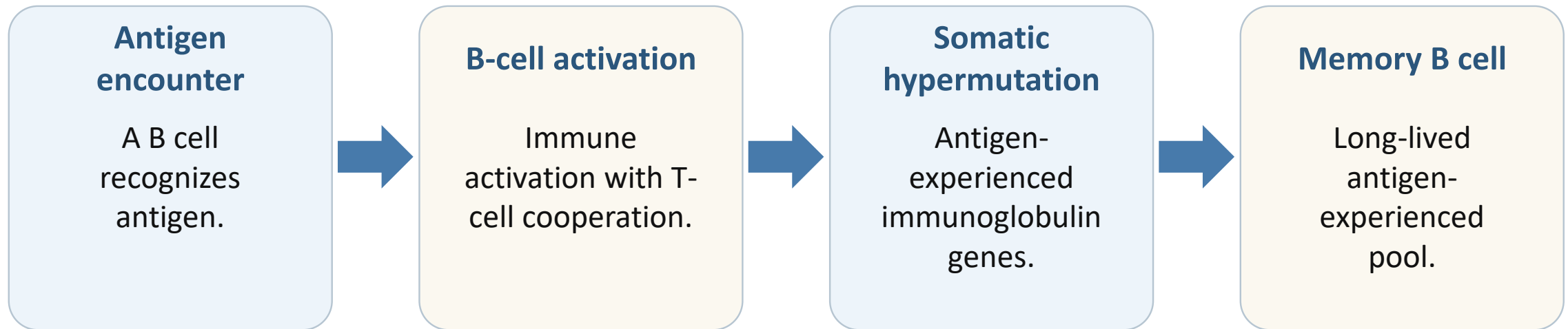
What does “MALT lymphoma” mean?

- MALT is mucosa-associated lymphoid tissue.
- Extranodal MZLs were first recognized at mucosal sites.
- The term MALToma is often applied to these extranodal tumors.
- Extranodal MZL also occurs in organs not normally rich in organized MALT.

Memory B-cell origin: The biologic clue

- Tumor immunoglobulin genes frequently show somatic hypermutation.
- Somatic hypermutation is a record of prior antigen-driven B-cell maturation.
- This favors an antigen-experienced, memory B-cell origin in many cases.
- The site and molecular background remain heterogeneous across MZLs.

From antigen exposure to a memory B cell



Why extranodal MZL is a distinctive model

Inflammatory setting

Often associated with chronic immune stimulation from infection or autoimmunity.

Prolonged localization

May remain confined to one organ for substantial periods.

Potential reversibility

Some lesions regress after removal of the inciting antigen.

These features connect etiology, natural history, and therapeutic response.

Organ-specific immune stimulation

Tissue	Associated inflammatory disorder	Extranodal MZL context
Stomach	Helicobacter-associated gastritis	Gastric MALT lymphoma
Salivary gland	Sjögren syndrome	Salivary extranodal MZL
Thyroid	Hashimoto thyroiditis	Thyroid extranodal MZL

Sjögren syndrome: The salivary gland pathway

- Chronic lymphocytic inflammation targets salivary and lacrimal glands.
- Early infiltrates contain a mixture of polyclonal B and T cells.
- A B-cell clone may acquire a growth advantage during sustained stimulation.
- A dominant clonal B-cell population can signal emergence of MZL.

Sjögren syndrome: Why lymphoma risk rises

- An autoimmune microenvironment supplies persistent lymphocyte activation.
- A strong increase in lymphoma risk in Sjögren syndrome.
- Clonal selection is thought to follow acquisition of somatic mutations.
- The lymphoma typically emerges in the chronically inflamed target gland.

Do not equate every clonal expansion with histologically established lymphoma.

Hashimoto thyroiditis and thyroid MZL

- Autoimmune thyroid inflammation provides ongoing local immune stimulation.
- Extranodal marginal zone lymphoma may develop in the thyroid gland.
- The organ-level link parallels salivary gland disease in Sjögren syndrome.
- A thyroid lymphoid infiltrate must be interpreted with its inflammatory context.

Helicobacter gastritis: The gastric association

- Chronic *Helicobacter pylori* infection produces persistent gastric inflammation.
- The associated immune response may generate organized lymphoid tissue.
- Most gastric MALT lymphomas arise in this inflammatory setting.
- Antigen removal is therapeutically relevant while growth remains dependent.

Gastric MALT is generally acquired

Normal stomach

Typically lacks organized mucosa-associated lymphoid tissue.

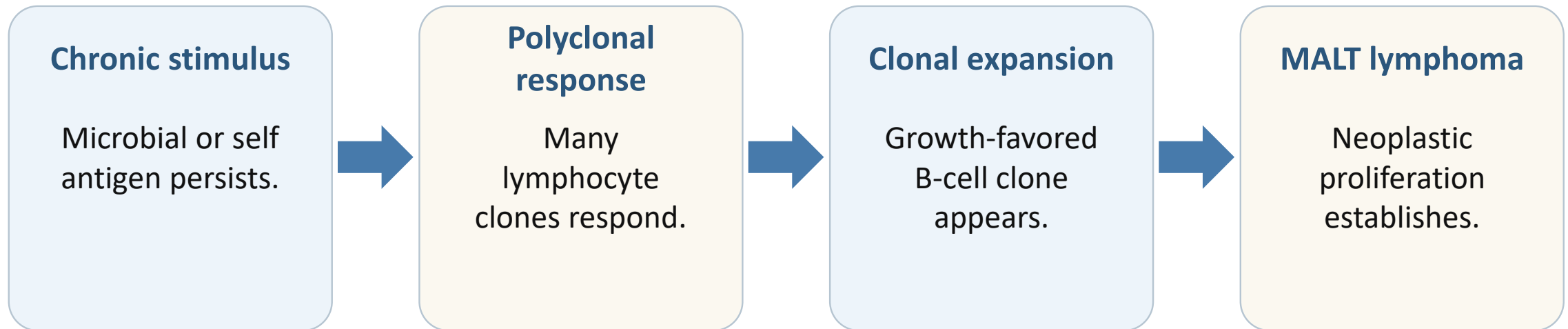
Persistent gastritis

Chronic inflammation recruits lymphocytes and can induce gastric MALT.

Clonal evolution

A neoplastic B-cell population may emerge from persistent immune stimulation.

Inflammation-to-lymphoma continuum



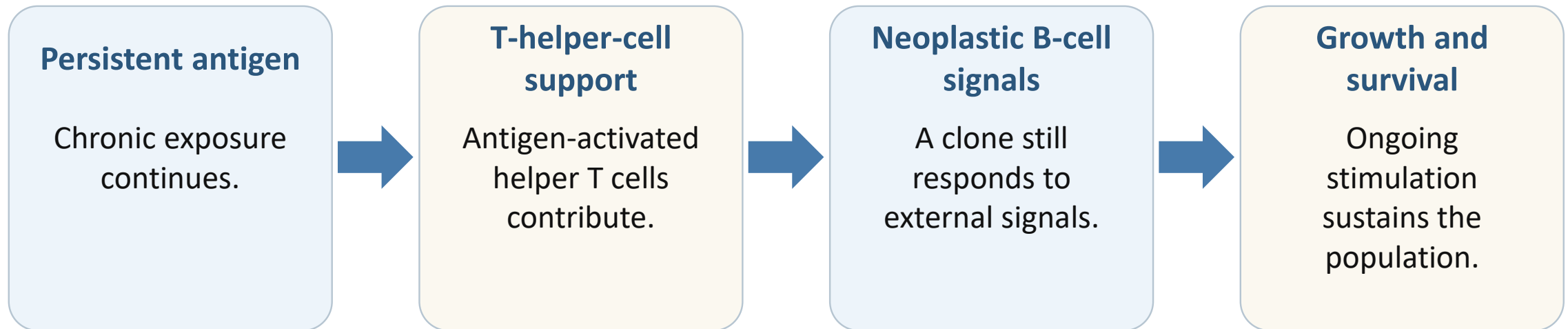
Stage 1: An initially polyclonal reaction

- Early chronic immune stimulation expands diverse reactive lymphocytes.
- Multiple B-cell clones may respond to the same persistent antigen source.
- Polyclonality belongs to the reactive end of the continuum.
- Polyclonality alone is not evidence of an established lymphoma.

Stage 2: A B-cell clone gains advantage

- Unknown initiating mutations are proposed to confer a selective benefit.
- A dominant B-cell population begins to emerge from a reactive background.
- Clonality provides useful evidence but is not sufficient by itself.
- Tissue architecture and clinical setting remain necessary for interpretation.

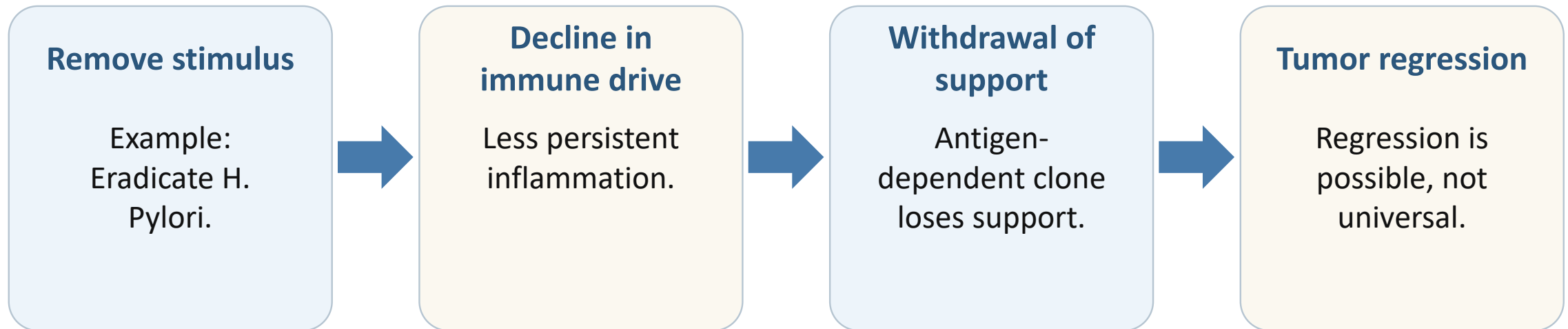
The antigen-dependent stage



Why T-helper cells matter early

- The early lymphoma clone may require signals from antigen-stimulated T cells.
- The immune microenvironment therefore remains part of its growth program.
- Removing antigen can suppress the upstream source of supportive signals.
- This dependency distinguishes early disease from genetically autonomous clones.

Antigen removal: A biologic intervention



Why H. Pylori eradication can work

- Antibiotics target the initiating organism, not the tumor directly.
- An antigen-dependent clone may regress when microbial stimulation ceases.
- This is a compelling demonstration of microenvironmental dependence.
- Response is not assured once the clone has acquired autonomous signaling.

Stage 3: Acquired antigen independence

- Additional mutations or translocations can confer growth autonomy.
- Downstream survival pathways remain active without antigen exposure.
- The clone no longer requires the original inflammatory stimulus.
- This model explains resistance to microbial eradication.

Antigen dependent versus antigen independent

Antigen-dependent phase

- External stimulus remains important.
- T-cell and receptor-linked signals support tumor survival.
- Withdrawal of antigen can produce regression.

Antigen-independent phase

- Lymphoma acquires constitutive growth/survival signaling.
- BCL10 or MALT1 pathway changes can drive autonomy.
- Eradication of the organism often fails to control tumor.

Why extranodal MZL may remain localized

- Prolonged restriction to an affected organ.
- Local antigenic stimulation provides a plausible selective niche.
- Late systemic spread can occur as tumor biology changes.
- Site of origin and extent of dissemination are separate clinical questions.

Late dissemination represents clonal evolution

- Some extranodal tumors eventually spread beyond their original site.
- Additional acquired alterations may promote more autonomous behavior.
- A previously localized lesion does not guarantee permanent localization.
- Clinical follow-up must account for possible change over time.

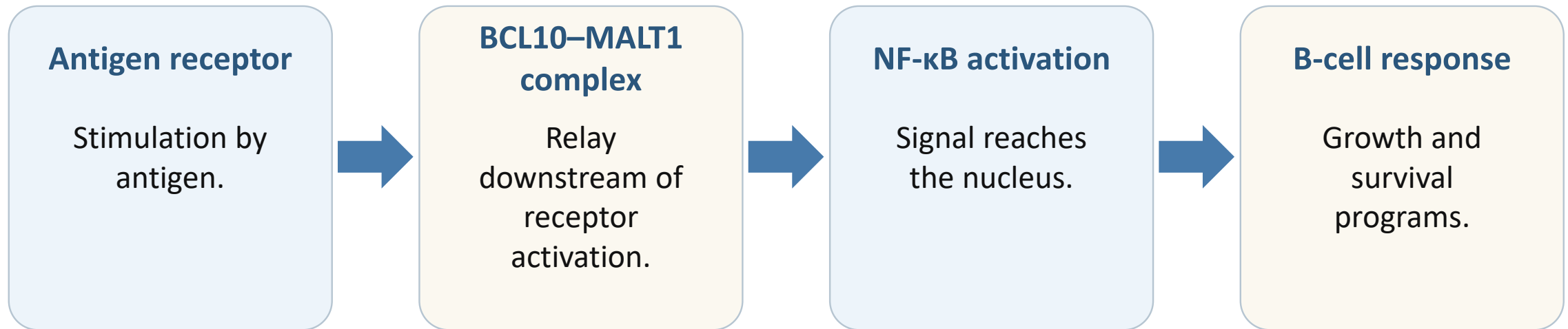
Progression to diffuse large B-cell lymphoma

- A subset of MALT lymphomas transforms to aggressive large B-cell lymphoma.
- Histology then resembles diffuse large B-cell lymphoma (DLBCL).
- This reflects further clonal evolution rather than ordinary reactive change.
- Growth pattern and cytologic size should be reassessed in evolving lesions.

NF- κ B: A survival-related transcription factor

- NF- κ B promotes transcriptional programs supporting B-cell survival.
- In lymphocytes, antigen receptor signaling can activate NF- κ B.
- Constitutive NF- κ B activity can sustain lymphoma cells without antigen.
- The pathway links external immune stimulation with genetic autonomy.

Normal antigen receptor–NF- κ B signaling



The BCL10–MALT1 signaling module

- BCL10 and MALT1 are proteins acting in a receptor-linked complex.
- The module participates in antigen-stimulated NF- κ B activation.
- Genetic lesions can increase signaling through this pathway.
- The shared end point is enhanced B-cell growth and survival.

Recurrent rearrangements in gastric MALT lymphoma

Rearrangement	Gene-level result	Core teaching implication
t(11;18)	API2–MALT1 fusion protein	Constitutive NF-κB activation
t(1;14)	Increased BCL10 expression	Constitutive NF-κB activation
t(14;18)	Increased MALT1 expression	Constitutive NF-κB activation
t(3;14)	Increased FOXP1 expression	Distinct transcription-factor route

FOXP1-related t(3;14) is distinct from the NF-κB-activating trio.

T(11;18): The API2–MALT1 fusion

- The chromosomal translocation juxtaposes genes on chromosomes 11 and 18.
- The resulting fusion protein includes API2 and MALT1 components.
- The fusion drives signaling that promotes constitutive NF- κ B activity.
- The molecular lesion supports antigen-independent survival.

T(1;14): Increased BCL10 expression

- Rearrangement involving the BCL10 locus can increase BCL10 abundance.
- BCL10 is a component of the lymphocyte receptor–NF- κ B pathway.
- Excess signaling activity helps bypass antigen dependence.
- This rearrangement is distinct from an API2–MALT1 fusion.

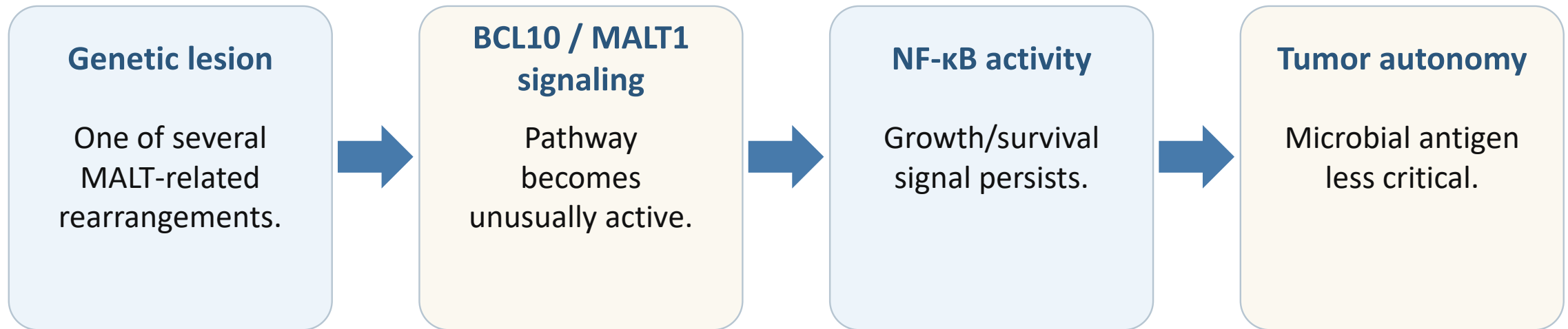
T(14;18): Increased MALT1 expression

- A subset of MALT lymphomas upregulates intact MALT1 through t(14;18).
- MALT1 contributes to NF- κ B-related antigen receptor signaling.
- This MALT-associated rearrangement is not synonymous with the BCL2 rearrangement of follicular lymphoma.
- The involved gene must be identified, not inferred from the numbers alone.

T(3;14): The FOXP1-associated route

- T(3;14) among gastric MALT lymphoma rearrangements.
- This juxtaposes FOXP1 with an immunoglobulin locus.
- FOXP1 transcription factor expression increases.
- The textbook separates it from the three rearrangements that directly cause constitutive NF- κ B activation.

Convergence on NF- κ B signaling



Pathway contrast: Stimulus versus genetic bypass

Before signaling autonomy

- Antigen receptor activation begins the cascade.
- BCL10 and MALT1 function downstream.
- Removing antigen may reduce pathway activity.

After genetic bypass

- Rearrangement increases pathway signaling.
- NF- κ B-related survival support becomes persistent.
- Removing antigen may no longer stop growth.

Molecular predictors of eradication resistance

- MALT1- or BCL10-associated translocations correlate with poor response to H. Pylori clearance.
- The biologic explanation is sustained signaling despite stimulus removal.
- Absence of a detected translocation does not guarantee response.
- A complete assessment also requires tissue extent and nodal status.

Other correlates of poor eradication response

Observation

Interpretive consequence

Extension into or through muscularis propria

Greater tissue penetration correlates with resistance

Lymph node involvement

More extensive disease correlates with resistance

MALT1/BCL10-related translocation

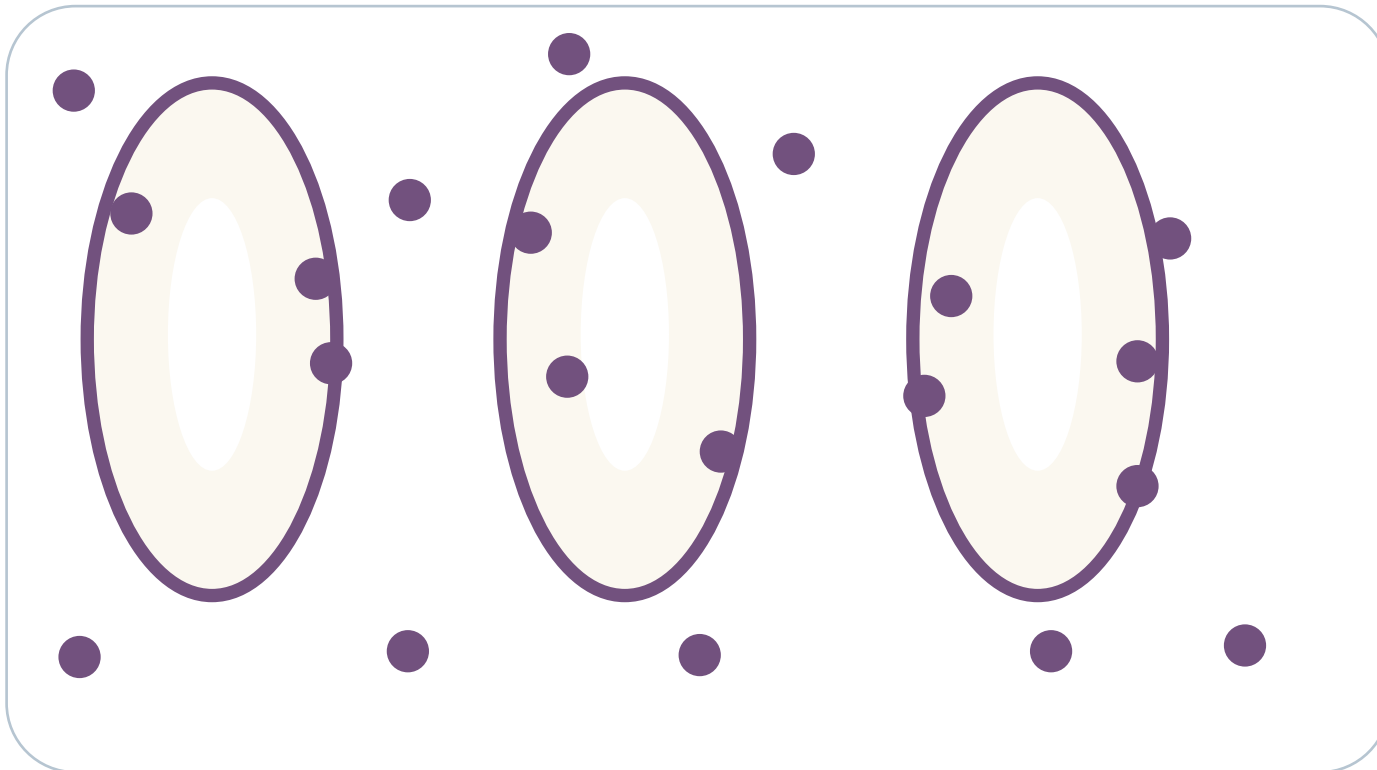
Antigen-independent signaling is more likely

Gastric MALT lymphoma: Lamina propria expansion

- Histology shows a dense lymphocytic infiltrate in the gastric lamina propria.
- Neoplastic cells may extend toward and into adjacent gastric glands.
- Reactive-appearing follicles may coexist with the infiltrate.
- The pattern must be interpreted against chronic gastritis.

Lymphoepithelial lesion: An architectural concept

Architectural schematic — not a histologic specimen



Glandular epithelium

Reactive or neoplastic lymphoid
infiltrate

Lymphoepithelial lesion = lymphoid
infiltration of gland epithelium

What makes a lymphoepithelial lesion?

- Lymphoma cells infiltrate glandular epithelium.
- This can distort or damage gland structure in the mucosal biopsy.
- The lesion is a strong morphologic clue in the appropriate tissue context.
- Diagnosis integrates histology, immunophenotype, and clinical findings.

An architectural finding is evidence—not a stand-alone molecular diagnosis.

Reactive follicles can persist in MALT lymphoma

- Some gastric MALT lymphomas contain reactive-appearing B-cell follicles.
- Follicles should not automatically be mistaken for follicular lymphoma.
- Architecture may therefore look deceptively reactive.
- The infiltrate around glands remains diagnostically important.

Plasmacytic differentiation is a recognized pattern

- A subset of gastric MALT lymphomas shows plasmacytic differentiation.
- This in approximately 40% of tumors.
- This feature can change the appearance of the infiltrate.
- Light-chain restriction may help establish a clonal B-cell population.

Morphologic context matters more than one feature

- Dense mucosal lymphocytes support—but do not prove—lymphoma.
- Lymphoepithelial lesions increase suspicion in the right context.
- Reactive follicles and plasma cells can complicate interpretation.
- Classification requires a coherent pattern of multiple findings.

B-cell lineage markers: CD19 and CD20

- Gastric MALT lymphomas express mature B-cell markers including CD19 and CD20.
- These markers establish lineage, not the specific MZL subtype.
- Marker expression is interpreted in the context of histology.
- No single pan-B-cell marker establishes MALT lymphoma.

CD5 and CD10: Useful negative evidence

- Gastric MALT lymphoma is usually CD5 negative and CD10 negative.
- This profile supports exclusion of several competing small B-cell lymphomas.
- Negative findings are supporting evidence rather than absolute proof.
- Interpretation must consider the entire staining panel.

CD43: A supportive but incomplete clue

- CD43 is expressed in a minority of gastric MALT lymphomas.
- Positivity in about 25% of cases.
- Because expression is variable, negativity cannot exclude lymphoma.
- A positive result may be diagnostically useful in context.

Immunoglobulin light-chain restriction

- A normal reactive infiltrate typically comprises multiple B-cell clones.
- Predominance of κ or λ expression supports clonality.
- Restriction is especially valuable when clear lymphoepithelial lesions are absent.
- A clonal pattern still requires clinicopathologic correlation.

Immunoglobulin heavy-chain rearrangements

- Molecular analysis may demonstrate a clonal IGH gene rearrangement.
- This can support lymphoma in a histologically equivocal sample.
- The assay addresses clonality rather than anatomic subtype by itself.
- It is not a substitute for morphology and immunophenotype.

Why a small gastric biopsy can be difficult

- H. Pylori gastritis and gastric MALT lymphoma often coexist.
- Symptoms and endoscopic appearances may overlap.
- A limited biopsy can undersample lymphoepithelial lesions.
- Ancillary studies are most useful when interpreted with adequate tissue.

Integrated diagnostic workflow for gastric MALT lymphoma

1. Clinical context

Persistent gastritis, symptoms, and H. Pylori status.

2. Architecture

Lamina propria infiltrate, follicles, gland infiltration.

3. Immunophenotype

CD19/CD20; Usual CD5–/CD10– pattern; CD43 if present.

4. Clonality if needed

Light-chain restriction or clonal IGH rearrangement.

A composite diagnosis is stronger than any isolated test.

Gastritis versus gastric MALT lymphoma

Finding	Reactive <i>Helicobacter</i> gastritis	Gastric MALT lymphoma
Inflammatory infiltrate	Expected in chronic infection	Dense lymphoid infiltrate also present
B-cell population	Generally polyclonal	Clonality may be demonstrable
Lymphoepithelial lesion	Not diagnostic on its own	An important morphologic clue
Ancillary tests	Not always required	Useful in equivocal biopsies

Small B-cell lymphoma differential

Feature	MALT lymphoma	Mantle cell lymphoma
Typical CD5	Negative in gastric MALT	Usually positive
Cell of origin	Often memory B cell	Usually naive mantle-zone B cell
Cyclin D1	Not defining feature	Typically high expression
Classic genetics	MALT1/BCL10 pathway lesions	t(11;14), CCND1 upregulation

T(14;18): A differential diagnostic trap

- Follicular lymphoma is often driven by an IGH–BCL2 rearrangement.
- Gastric MALT lymphoma may show t(14;18) involving IGH and MALT1.
- Identical chromosome numbers can refer to distinct partner genes.
- A precise gene-level assay resolves the biologic meaning.

Gastric presentation: Symptoms are nonspecific

- Dyspepsia and epigastric pain are common presenting symptoms.
- Weight loss may occur but is not required.
- Symptoms overlap with H. Pylori-associated gastritis.
- A tissue diagnosis cannot be inferred from symptoms alone.

Gastrointestinal bleeding as a presentation

- Hematemesis or melena can be present in gastric MALT lymphoma.
- Bleeding symptoms require appropriate clinical assessment.
- Endoscopic changes are not unique to lymphoma.
- Histology anchors the distinction from other gastric lesions.

Disease extent affects clinical interpretation

- Many extranodal MZLs remain localized for prolonged periods.
- Lymph node involvement suggests more extensive disease.
- Muscularis propria invasion is associated with poorer eradication response.
- Local response and systemic spread must be followed separately.

Transformation: Histology and genetics

- Some low-grade MALT lymphomas progress to DLBCL.
- Additional lesions such as inactivation of genes encoding p53 or p16 may accompany transformation.
- This changes growth behavior beyond the usual indolent phenotype.
- Emergent large-cell areas should not be dismissed as ordinary MALT morphology.

Clinical application I: Antigen-dependent disease

Hypothetical case

A patient with chronic H. Pylori gastritis has a biopsy-supported gastric MALT lymphoma. Disease remains confined to the stomach, without an identified MALT1/BCL10 translocation.

Why might bacterial eradication lead to lymphoma regression?

Clinical application I: Reasoning

- Persistent microbial antigen may sustain the lymphoma through helper-cell signals.
- Eradication can remove the initiating immune stimulus.
- An antigen-dependent clone may then regress.
- Molecular testing and localized stage do not make regression certain.

Clinical application II: Biologic nonresponse

Hypothetical case

A gastric MALT lymphoma carries a rearrangement causing persistent BCL10–MALT1–NF- κ B signaling. H. Pylori is cleared, but the lymphoma persists.

What biologic feature best explains this outcome?

Clinical application II: Reasoning

- The tumor can sustain survival signaling downstream of antigen recognition.
- Removal of the organism no longer switches off the pathway.
- Constitutive NF- κ B activity is a central mechanistic explanation.
- A persistent lesion requires reassessment rather than assuming eradication failure.

Clinical application III: Autoimmune setting

Hypothetical case

A patient with Sjögren syndrome develops a persistent enlarging salivary gland lesion with a dense B-cell infiltrate and supportive evidence of clonality.

How does chronic autoimmunity connect to lymphoma emergence?

Clinical application III: Reasoning

- The gland contains a long-standing, activated lymphocyte population.
- Repeated stimulation may favor a mutation-bearing B-cell clone.
- Clonality supports a neoplastic possibility but needs tissue-context assessment.
- The clinical setting is characteristic for extranodal MZL.

Clinical application IV: The rearrangement pitfall

Hypothetical case

A mature B-cell lymphoma carries a reported t(14;18) rearrangement. A trainee assumes that every t(14;18) means follicular lymphoma.

What missing information changes this interpretation?

Clinical application IV: Reasoning

- Chromosomal breakpoints must be translated into the involved genes.
- IGH–BCL2 supports the canonical follicular lymphoma pathway.
- IGH–MALT1 is described in a subset of MALT lymphomas.
- Morphology and a gene-specific result remain essential.

Three anatomic groups: What this lecture established

MZL group	Established core information	Interpretive emphasis
Nodal	A mature B-cell MZL arising in lymph nodes	Interpret findings in nodal tissue context
Splenic	A mature B-cell MZL arising in spleen	Interpret findings in splenic tissue context
Extranodal	Often inflammation-associated; can remain localized	Gastric MALT is a well-characterized example

Integrating the pathology

- MZL is an anatomic family of mature, often antigen-experienced B-cell tumors.
- Persistent immune stimulation can precede extranodal MALT lymphoma.
- BCL10/MALT1-driven NF- κ B signaling explains genetic autonomy.
- Gastric morphology and clonality support diagnosis.
- Antigen dependence, tissue extent, and clonal progression affect behavior.

Selected textbook references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th ed. (2026): Chapter 13, Marginal Zone Lymphomas.
- Same textbook: Chapter 17, Gastrointestinal Lymphoma (gastric MALT morphology, genetics, and diagnosis).
- Same textbook: Sjögren syndrome section (autoimmunity and lymphomagenesis).
- Same textbook: Chapter 13, mature B-cell neoplasms (context for differential diagnosis).