
Mechanisms of Metaplasia

How tissue stress redirects cell differentiation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

By the end of this lecture, learners should be able to:

- Distinguish the two mechanistic routes to metaplasia.
- Trace environmental signals to altered differentiation programs.
- Explain the retinoic-acid example of transcriptional control.
- Relate lineage substitution to tissue function and cancer risk.

Metaplasia among cellular adaptations

Metaplasia changes differentiated cell identity rather than simply cell size or number.

Adaptation	Primary change	Illustrative cause
Hypertrophy	Cell size increases	Increased workload
Hyperplasia	Cell number increases	Hormonal or growth-factor signals
Atrophy	Cell and organ size decrease	Disuse or reduced nutrients
Metaplasia	Differentiated cell type is replaced	Chronic irritation

Metaplasia: Reversible cell-type replacement

One differentiated epithelial or mesenchymal cell type is replaced by another.



"Reversible" describes the adaptive phenotype; It does not mean persistent injury is harmless.

An adaptation can impose a functional cost

The replacement lineage may be more stress-resistant yet less specialized.

Adaptive benefit

- Survives a hostile local environment
- Can preserve an epithelial covering

Physiologic cost

- Specialized functions can be lost
- Protection against infection may diminish

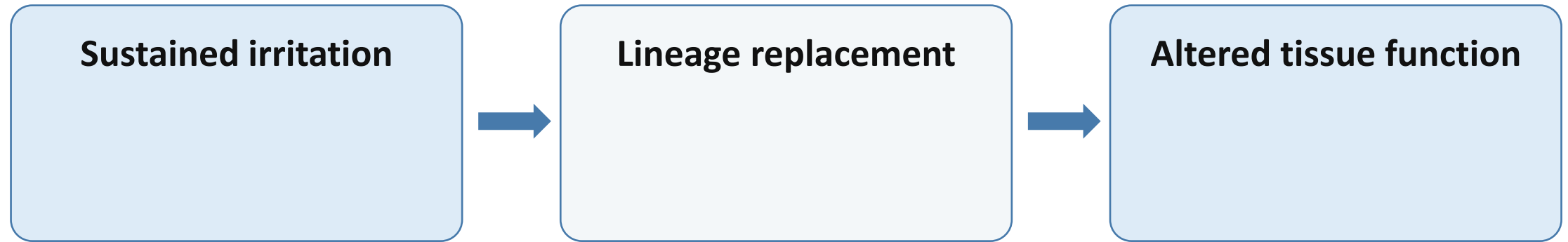
Metaplasia spans two tissue categories

The source describes both epithelial and connective-tissue forms.

Feature	Epithelial	Connective-tissue
What changes	Lining cell type	Mesenchymal tissue type
Examples	Bronchial squamous; Barrett	Bone in skeletal muscle
Cancer association	May increase with persistent injurious influences	Not linked to increased risk in source

Reversibility is not the same as harmlessness

A potentially reversible response may still reduce function during ongoing exposure.

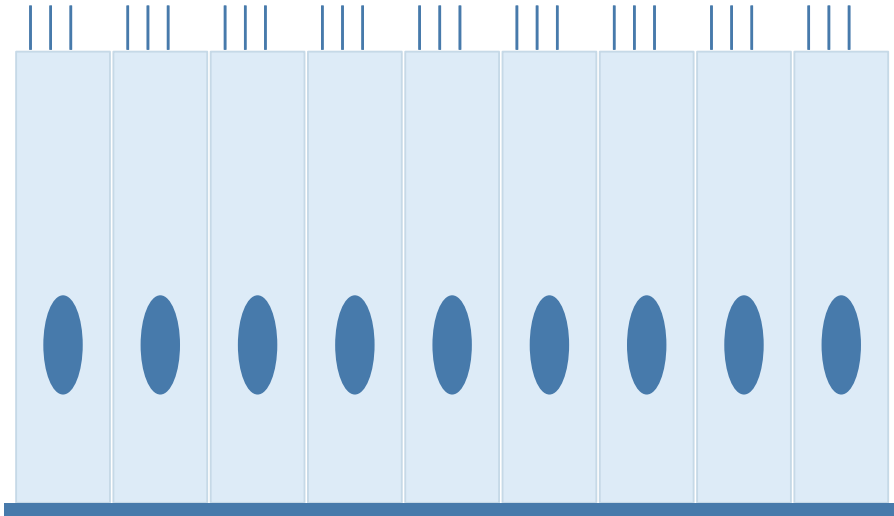


In the respiratory tract, the squamous phenotype is durable but loses normal mucociliary defenses.

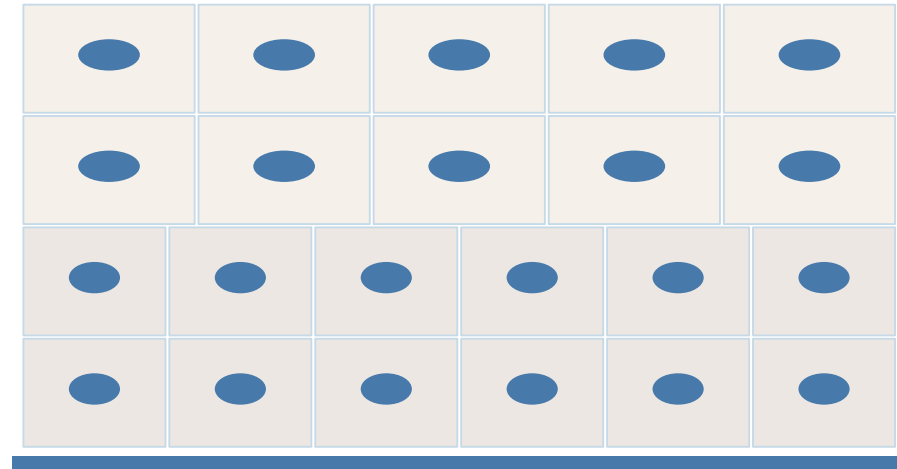
Metaplasia is an outcome at tissue level

Metaplasia is recognized as an altered epithelial population across a lining.

Ciliated columnar lining



Stratified squamous lining



Schematic illustration

Schematic: Contrasting mature cell arrangements illustrates the outcome, not the lineage mechanism.

The microenvironment creates selective pressure

Sustained stress can make an existing specialized phenotype disadvantageous.



Different tissues can respond to different local combinations of environmental signals.

Two mechanistic routes to metaplasia

Two alternatives—not obligatory sequential stages.

Route 1

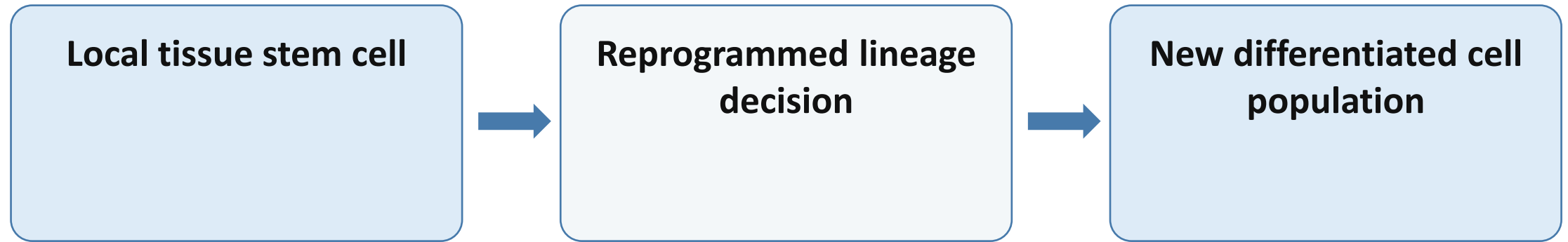
- Reprogramming of local tissue stem cells
- New progeny follow a different differentiation pathway

Route 2

- Colonization from adjacent sites
- Differentiated cells from a neighboring population populate tissue

Route 1 begins with a resident stem-cell pool

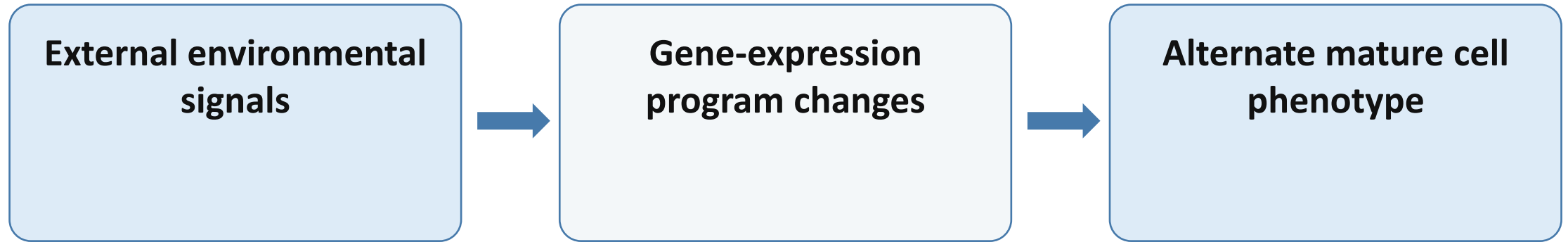
Local tissue stem cells can change the differentiation outcome of their progeny.



Mechanism: Altered fate choice at the stem/progenitor level.

Stem-cell reprogramming redirects progeny

The defining alteration is which differentiation program becomes expressed.



Differentiation changes arise from transcriptional regulation of the developing cell population.

Changed differentiation is not cell enlargement

Compare stem-cell fate change with growth responses in the same chapter.

Question	Metaplasia	Hypertrophy / hyperplasia
What is altered?	Type of mature progeny	Size / abundance
Central event	Differentiation pathway shift	Growth response
Tissue output	Different differentiated phenotype	More cell mass / cells

Direct conversion of mature cells is not the proposed route

The mechanism section explicitly rejects a simple mature-cell identity switch.

Not the described model

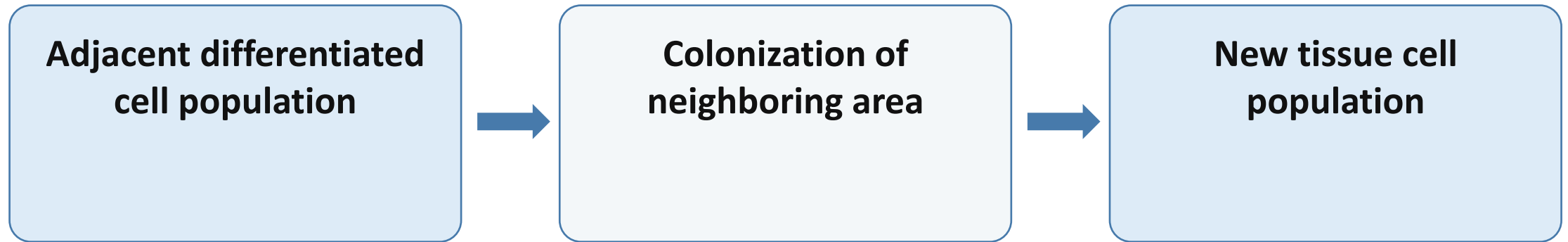
- One fully differentiated cell directly changes its phenotype
- No new progenitor or incoming population

Routes

- Differentiation of resident stem-cell descendants
- Colonization by cells from adjacent tissue

Route 2 uses a neighboring cell population

Metaplasia may arise when differentiated cells colonize from an adjacent site.



This is an alternative mechanism, not proof that every metaplastic lesion follows this route.

Colonization is spatially distinct from reprogramming

The two routes differ in the cellular source of the replacement population.

Resident-cell route

- Origin is within the affected tissue
- Local stem-cell differentiation is redirected

Adjacent-cell route

- Origin is a neighboring differentiated population
- The new cells occupy an adjacent site

Compare the two mechanistic routes

Either route can produce a new differentiated population.

Dimension	Stem-cell reprogramming	Adjacent-site colonization
Starting population	Local tissue stem cells	Adjacent differentiated cells
Core change	Differentiation pathway	Cell population occupying the site
Common result	Changed mature phenotype	Changed mature phenotype

Both routes depend on environmental signals

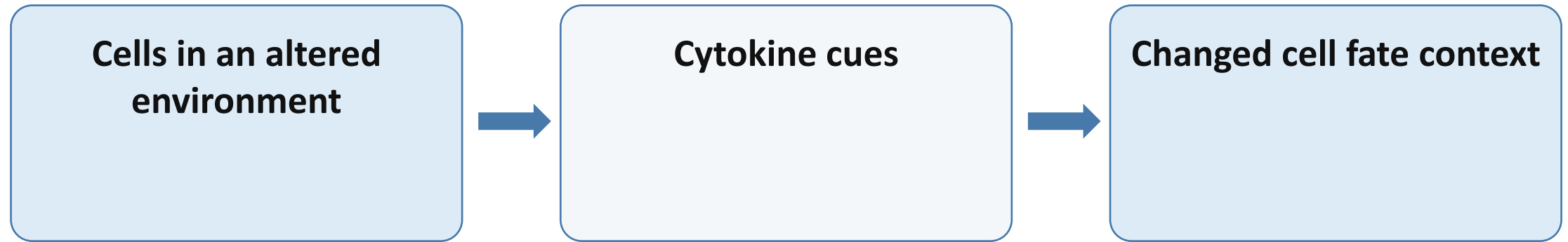
Cytokines, growth factors, and extracellular-matrix components create contextual cues.



The three signal categories contribute to the local setting for cell-fate change.

Cytokines are one class of instructive signals

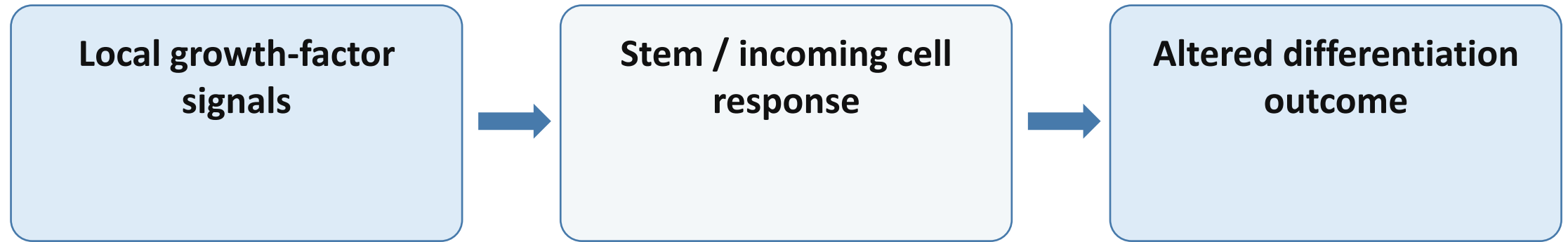
Locally generated cytokine signals form part of the metaplastic microenvironment.



Cytokines participate in a larger tissue signaling environment.

Growth factors participate in cell-fate cues

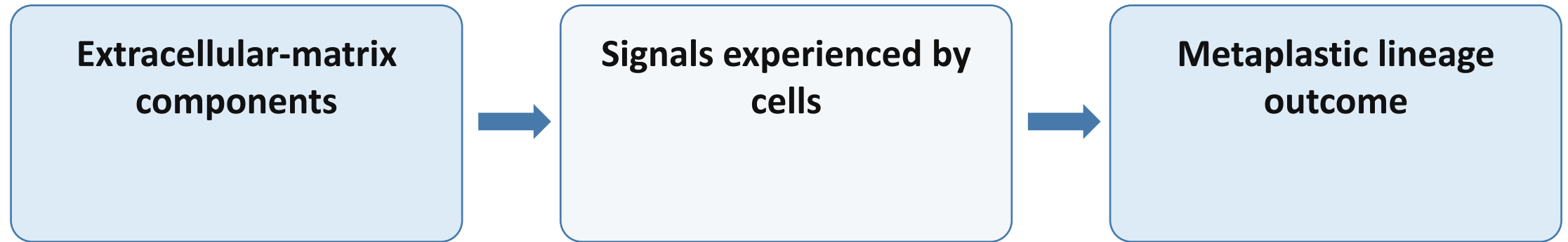
Growth factors are named among extracellular influences on metaplastic change.



Contextual regulation—not a single obligatory growth factor.

Extracellular matrix is part of the signal field

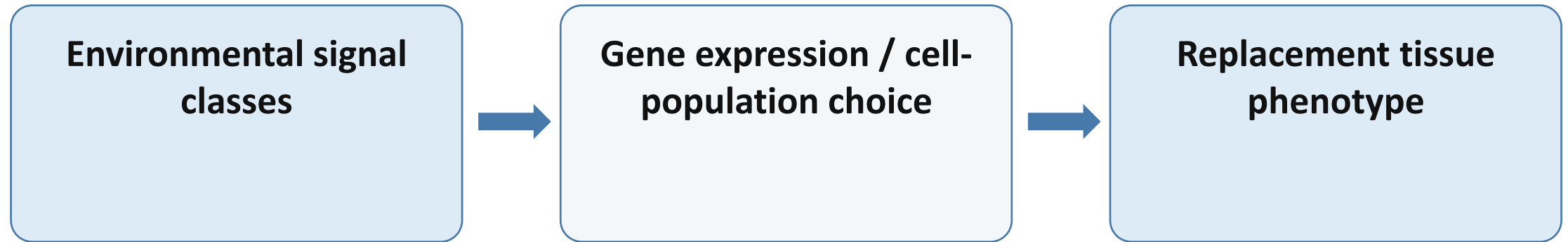
The matrix is a biologically active component of the environment.



Matrix-derived cues accompany growth-factor and cytokine signals.

Microenvironmental inputs converge on fate

Multiple tissue signals help determine which differentiation program is favored.



Cell-fate responses depend on both the signals and the tissue that receives them.

External stimuli alter gene expression

In stem-cell reprogramming, external cues promote genes that guide specific differentiation.



The observed metaplastic phenotype is downstream of a changed transcriptional program.

Cell phenotype follows a differentiation program

New differentiation programs alter the identity of the mature cell population.

Upstream control

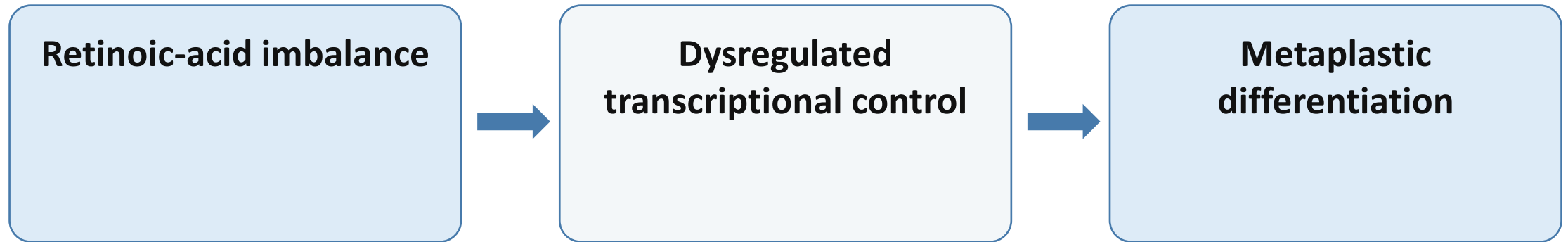
- Microenvironmental stimuli
- Transcriptional regulation
- Progenitor differentiation

Visible outcome

- Replacement mature-cell type
- Different tissue architecture
- Changed specialized function

Transcription factor dysregulation links cue to fate

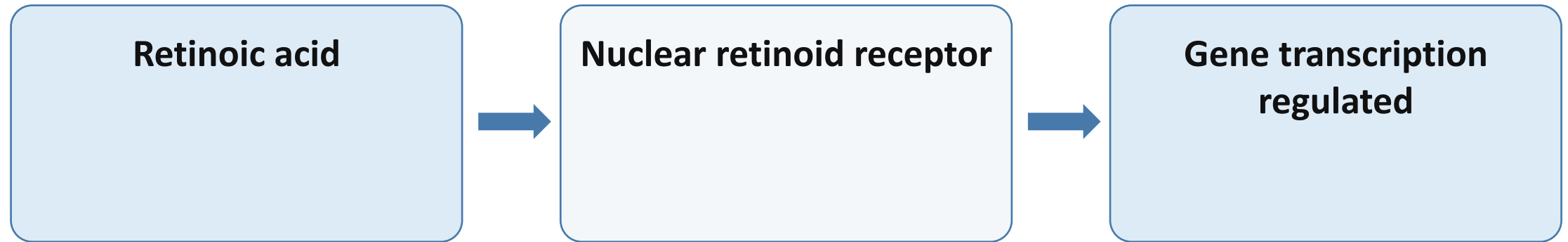
Retinoic-acid signaling provides a specific example of altered transcriptional regulation.



Retinoid signaling is one demonstrated example of transcriptional control of differentiation.

Retinoic acid directly regulates transcription

Retinoic acid acts through nuclear retinoid receptors.



These transcriptional effects can influence differentiation of stem-cell-derived progenitors.

Both retinoid deficiency and excess can cause change

A differentiation program may be disrupted in either direction of retinoid imbalance.

Deficiency

- A recognized cause of metaplasia
- Squamous change described in respiratory epithelium and cornea

Excess

- Also described as a cause of metaplasia
- The resulting phenotype depends on tissue context

Retinoids influence stem-cell-derived progenitors

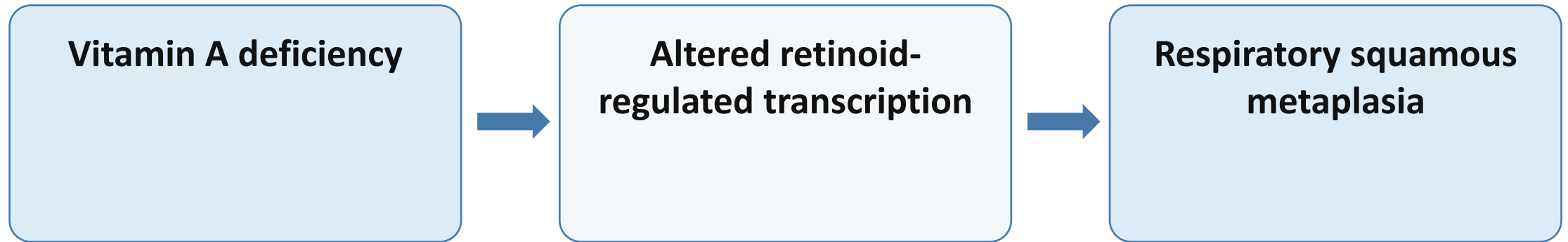
Nuclear retinoid receptor signaling can affect progenitor differentiation.



Connect ligand → nuclear receptor → transcription → progenitor fate.

Retinoid deficiency: Respiratory example

Vitamin A deficiency can induce squamous metaplasia of respiratory epithelium.



An environmental nutritional deficit can modify a transcription-dependent fate decision.

Retinoid deficiency: Corneal consequences

The same deficiency-associated switch can involve the ocular surface.

Observed tissue response

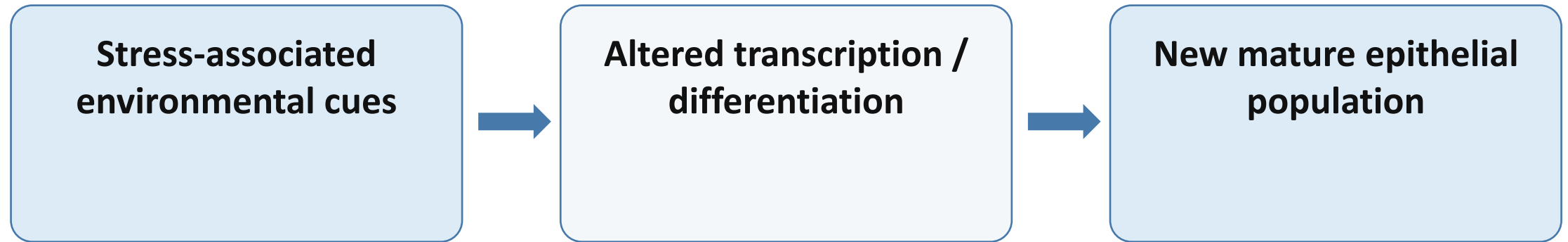
- Squamous metaplasia of the cornea
- Abnormal surface differentiation

Clinical importance

- Can be severely detrimental to vision
- A protective substitution may not be functionally appropriate

Integrating the stem-cell reprogramming route

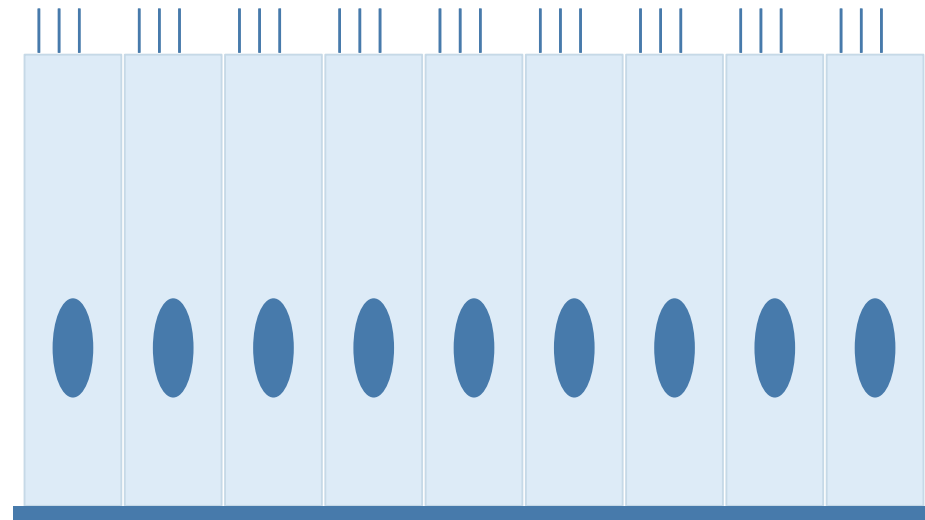
A mechanistic sequence supported by the Robbins text.



Clinical examples illustrate outcomes, but lineage origin is not established for each example.

Normal bronchial epithelium is specialized

Ciliated columnar epithelium combines mucus production with ciliary activity.



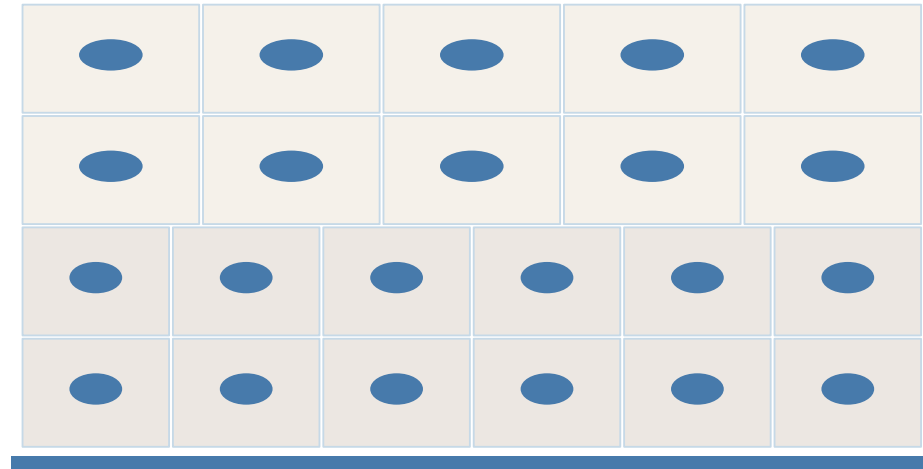
Basement membrane

Schematic illustration

Normal bronchial lining: Both mucus secretion and ciliary action contribute to host defense.

Squamous epithelium favors physical resilience

Stratified squamous lining is more robust in an adverse environment.



Basement membrane

Schematic illustration

In metaplasia, increased durability can come at the expense of specialized columnar functions.

Smoking causes sustained bronchial irritation

Habitual cigarette smoking is the textbook example of airway epithelial stress.

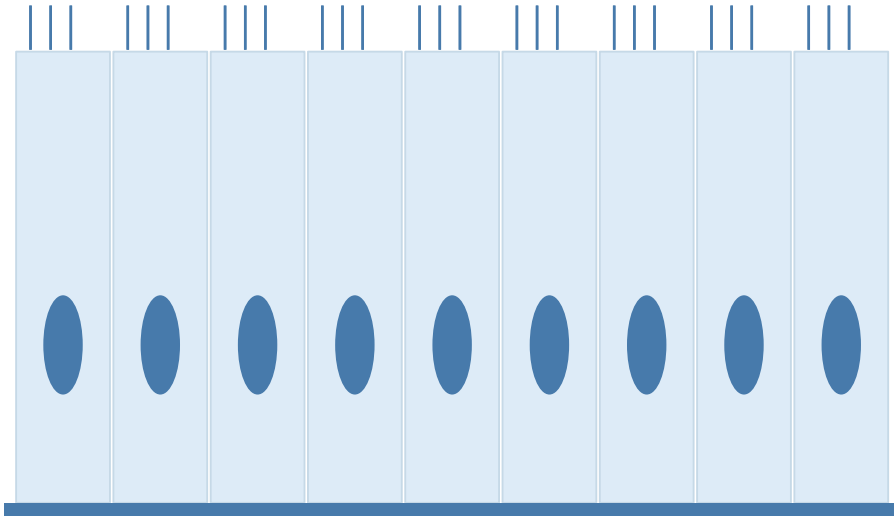


The replacement involves ciliated columnar cells becoming a stratified squamous lining at tissue level.

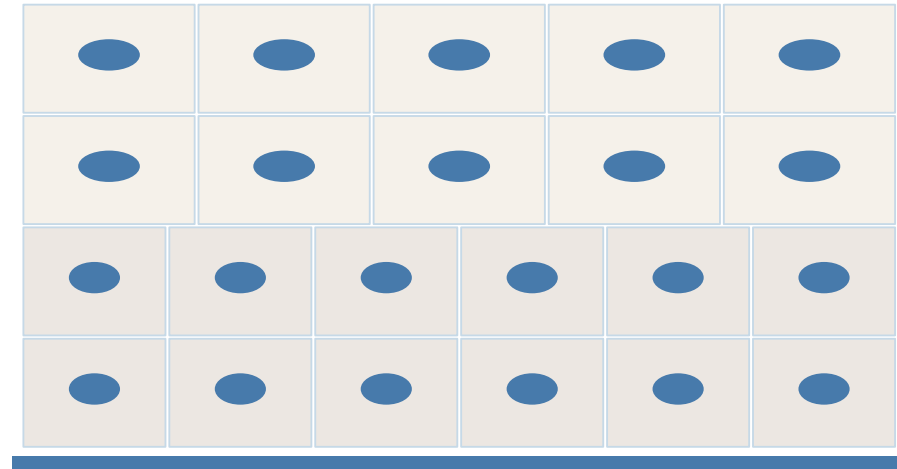
Bronchial squamous metaplasia: Architectural shift

A sheet of columnar cells is replaced by multiple layers of squamous cells.

Ciliated columnar lining



Stratified squamous lining



Schematic illustration

Columnar specialization is lost when a stratified squamous covering replaces the bronchial lining.

Squamous substitution improves durability

Relative resistance to chronic irritation helps explain why the new phenotype persists.

Original lining

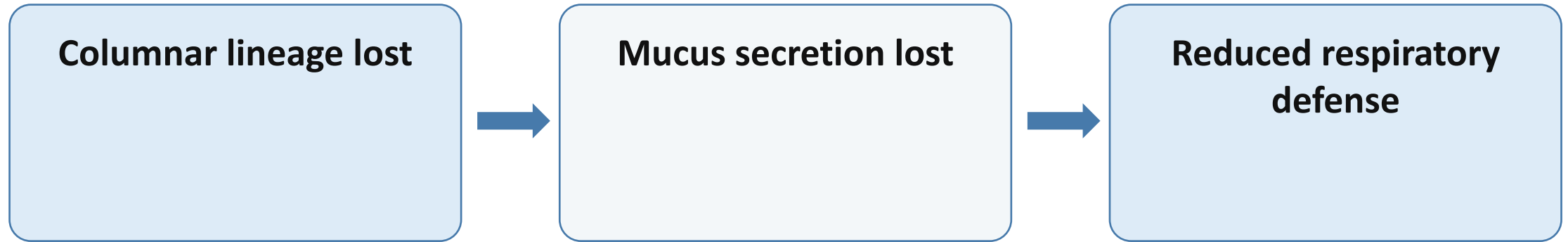
- Specialized ciliated columnar cells
- Vulnerable to sustained adverse exposure

Metaplastic lining

- Stratified squamous cells
- More durable in the same stress context

Loss of mucus secretion is part of the cost

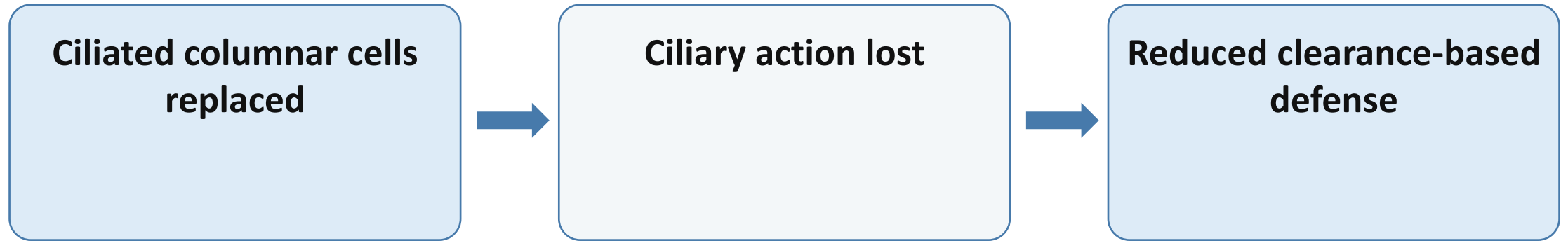
The replacement is not functionally equivalent to normal respiratory epithelium.



Loss of mucus secretion illustrates a critical functional cost of epithelial substitution.

Loss of ciliary action is a separate cost

Squamous replacement abolishes the ciliary function of the original lining.



Durability does not substitute for ciliary protection against infection.

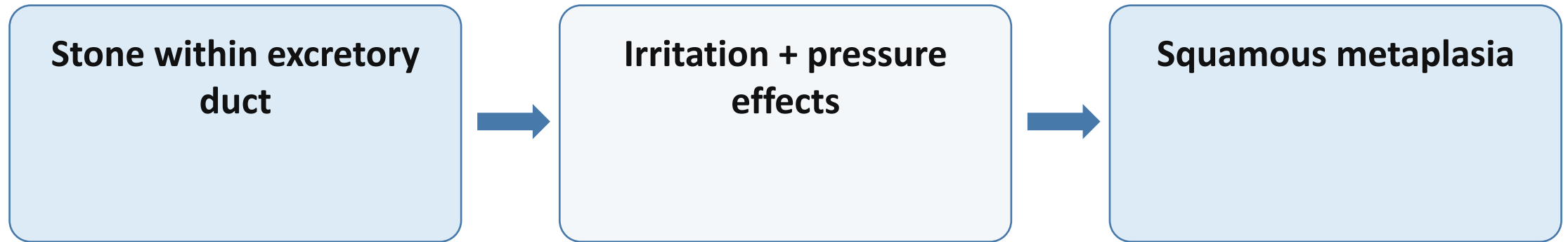
The airway trade-off links morphology to function

Why bronchial metaplasia can be clinically unfavorable.

Epithelial property	Normal columnar	Squamous metaplasia
Architecture	Specialized ciliated cells	Stratified squamous cells
Mucus secretion	Present	Lost
Ciliary action	Present	Lost
Stress tolerance	Less durable under chronic irritation	More durable

Ductal stones can cause squamous replacement

Irritation and pressure from stones can alter secretory ductal epithelium.



Salivary-gland, pancreatic and bile ducts are the textbook ductal examples.

Mechanical injury is another metaplastic setting

The ductal example differs from smoking but converges on similar epithelial substitution.

Bronchus

- Sustained inhaled irritation
- Ciliated columnar → squamous

Excretory duct

- Stone-related irritation and pressure
- Secretory columnar → squamous

Different exposures can converge on one phenotype

Metaplasia depends on tissue context—not a single required insult.

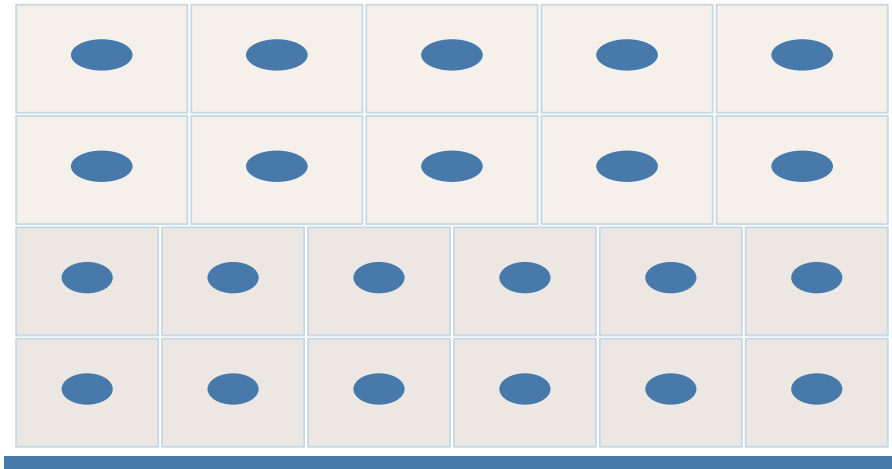


These examples share an endpoint; Robbins does not assert they use identical molecular pathways.

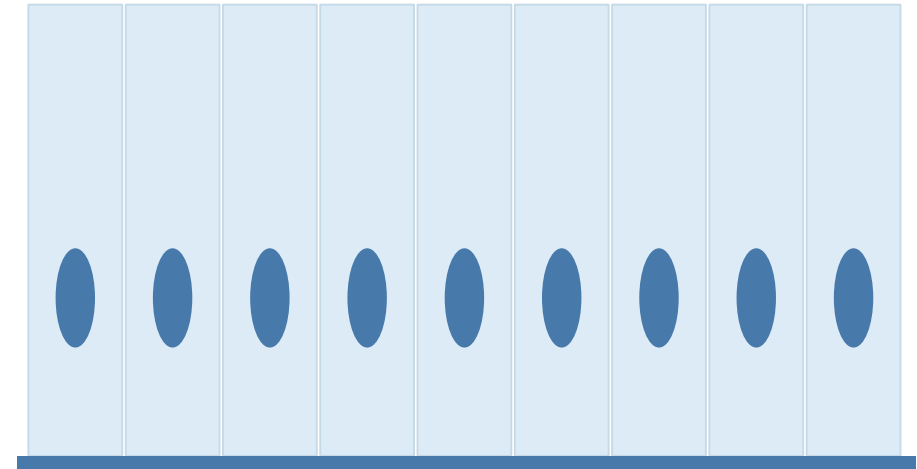
Barrett esophagus reverses epithelial direction

Esophageal squamous epithelium can be replaced by intestinal-like columnar cells.

Squamous esophageal lining



Intestinal-like columnar lining



Schematic illustration

Schematic: Opposite direction from the common airway columnar-to-squamous example.

Refluxed gastric acid is the Barrett stimulus

Exposure to gastric acid is the specified environmental influence.



Barrett esophagus illustrates metaplasia from squamous toward columnar differentiation.

Barrett epithelium has a different identity

Cell-type replacement changes the character of the esophageal lining.

Before replacement

- Native squamous epithelium
- Stratified epithelial arrangement

After replacement

- Intestinal-like columnar cells
- Gland-forming cancer is the characteristic linked malignancy

The direction of metaplasia is site-specific

The result depends on exposure and original tissue.

Site	Starting lining	Replacement lining	Stimulus
Bronchus	Ciliated columnar	Stratified squamous	Chronic smoke irritation
Esophagus	Squamous	Intestinal-like columnar	Gastric acid reflux
Excretory duct	Secretory columnar	Squamous	Stone irritation / pressure

Persistent influences can increase epithelial risk

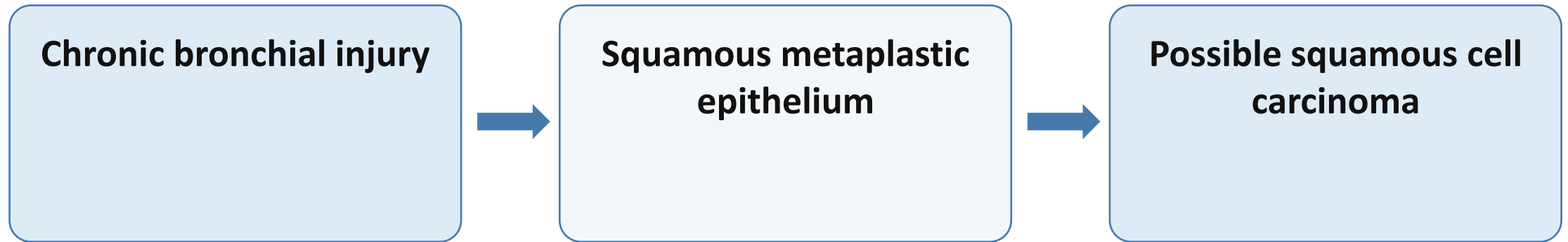
The same influences that predispose to metaplasia may later initiate malignancy.



A possible association is not an inevitable progression or a cancer diagnosis.

Bronchial squamous change and carcinoma

The textbook links persistent risk conditions to squamous carcinoma in affected lung areas.



The cancer relationship pertains to persistent carcinogenic influences, not a claim that every metaplasia becomes malignant.

Barrett-associated cancer is typically gland-forming

The phenotype of associated cancer reflects the metaplastic epithelial setting.



This association differs from the squamous carcinoma linked to affected bronchial epithelium.

Metaplasia is not synonymous with cancer

Separate an adaptive lineage change from malignant transformation.

Metaplasia

- Replacement differentiated phenotype
- May be reversible
- Not intrinsically a malignancy

Cancer risk context

- Some persisting epithelial influences carry risk
- Malignant transformation is a potential later outcome
- No inevitable time course is specified

Mesenchymal metaplasia has a distinct pattern

Connective-tissue metaplasia creates mesenchymal tissues in unusual locations.

Possible tissue outcomes

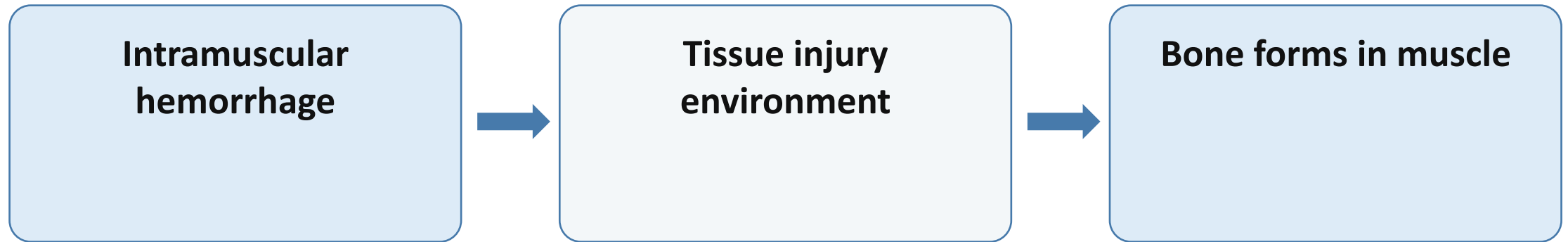
- Cartilage
- Bone
- Adipose tissue

Mechanistic context

- May follow local injury
- Not as clearly adaptive as epithelial metaplasia
- Different cancer-risk association

Myositis ossificans: Bone within muscle

An injury-related example of connective-tissue metaplasia.



The chapter uses myositis ossificans as an illustrative example of bone formation after hemorrhage.

Epithelial and mesenchymal risks differ

The source explicitly distinguishes their malignant associations.

Question	Epithelial metaplasia	Connective-tissue metaplasia
Typical setting	Chronic irritation	Tissue injury
Function	Durable replacement may cost specialization	Not clearly adaptive
Increased cancer risk	Can be associated with persistent influences	Not associated with increased risk

Clinical vignette: Chronic smoker

A habitual smoker has replacement of the ciliated bronchial lining by stratified squamous epithelium.

Questions for interpretation

- What is the direction of epithelial replacement?
- Which specialized functions are lost?
- Why can the new lining persist despite a functional cost?

Smoker vignette: Mechanism and consequences

Answer the case by linking exposure, lineage and physiology.

Morphologic response

- Columnar → squamous metaplasia
- More durable stratified lining

Functional impact

- Mucus secretion lost
- Ciliary activity lost
- Infection protection impaired

Clinical vignette: Chronic acid reflux

An individual with long-standing gastric acid reflux has intestinal-like columnar cells replacing esophageal squamous epithelium.

Questions for interpretation

- Name the metaplastic direction.
- Identify the environmental exposure.
- Which carcinoma type is linked to this field?

Reflux vignette: Mechanism and risk

The exposure is gastric acid and the replacement phenotype is columnar.

Epithelial change

- Squamous → intestinal-like columnar
- Barrett esophagus

Clinical correlation

- Continued injurious influence may confer risk
- Typical linked cancer: Adenocarcinoma

Clinical vignette: Hemorrhage in muscle

After an intramuscular hemorrhage, bone forms in a tissue normally lacking bone.

Questions for interpretation

- Is this epithelial or connective-tissue metaplasia?
- What term is used for this example?
- Does Robbins associate it with increased cancer risk?

Muscle vignette: Interpret the finding

Bone arising in muscle is the illustrative mesenchymal form.

Classification

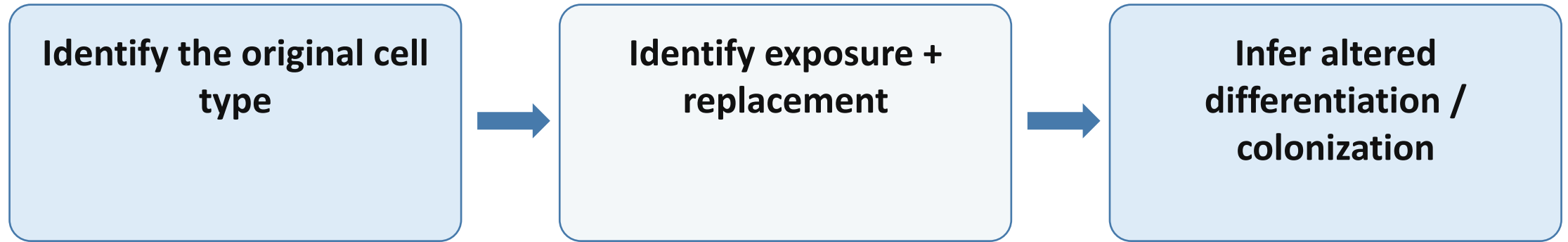
- Connective-tissue metaplasia
- Example: Myositis ossificans

Interpretation

- May result from tissue injury
- Not clearly an adaptive improvement
- Not linked to increased cancer risk in this chapter

A useful mechanism-based reasoning sequence

Work from the tissue setting toward a defensible explanation.



Do not assign a particular route or molecular mediator when the source does not resolve it.

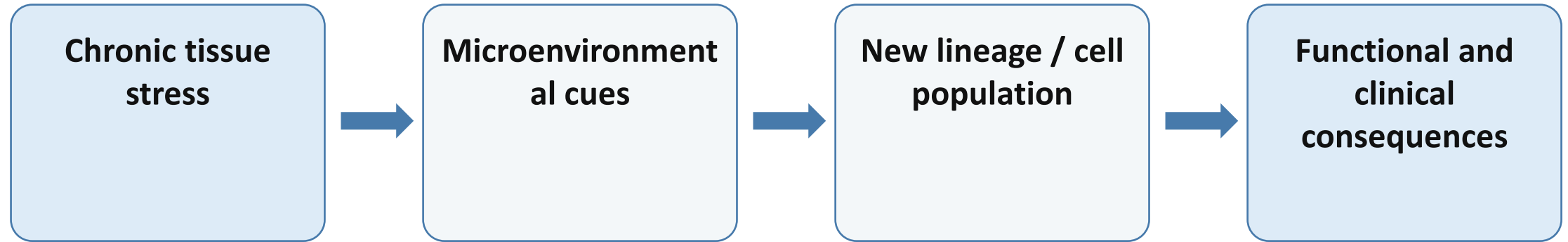
Common interpretive errors

Avoid extrapolating beyond what the source establishes.

Incorrect inference	Source-consistent interpretation
Every mature cell directly switches identity	Stem-cell reprogramming or adjacent colonization
Squamous change is purely protective	Specialized respiratory defenses are lost
Metaplasia always causes carcinoma	Cancer is a possible outcome under persistent influences
All forms carry the same cancer risk	Connective-tissue change differs from epithelial change

Integrated model: Signals to tissue outcome

A compact synthesis of the causal logic.



Routes may involve local stem-cell programming or colonization; Outcome varies by site.

Four principles to retain

Mechanisms explain how a new phenotype replaces the original tissue lining.

- Replacement proceeds by stem-cell reprogramming or adjacent-site colonization.
- Cytokines, growth factors and extracellular matrix provide contextual signals.
- Gene expression and retinoid-dependent transcription help determine progenitor fate.
- Better stress tolerance may sacrifice specialized function and, in some epithelial settings, accompany increased cancer risk.

Primary reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).

- Cell Injury, Cell Death, and Adaptations.
- Metaplasia; Mechanisms of Metaplasia.
- Mechanistic understanding depends on source-based interpretation of tissue context.