

Smoking-Related Interstitial Diseases

Desquamative interstitial pneumonia • Respiratory bronchiolitis–associated ILD

Anatomic pattern • Morphology • Clinical significance

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Locate smoking-associated changes within the respiratory acinus
- Recognize the defining histologic features of DIP and RB-ILD
- Interpret the clinical threshold between respiratory bronchiolitis and RB-ILD
- Compare disease distribution, functional effects and smoking cessation outcomes

Smoking may produce obstructive and interstitial disease

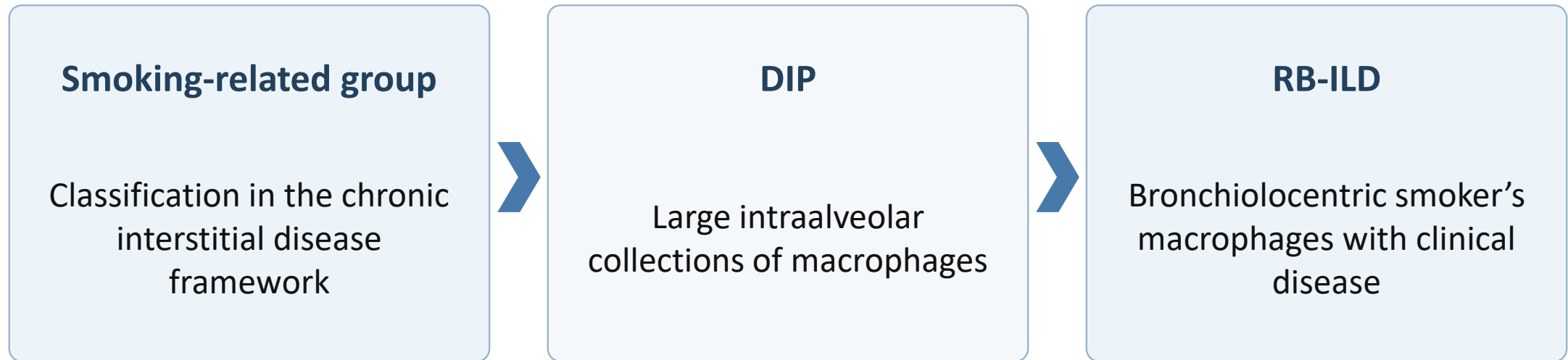
Obstructive disorders

- Emphysema
- Chronic bronchitis
- Airway-predominant physiologic impairment

Interstitial disorders

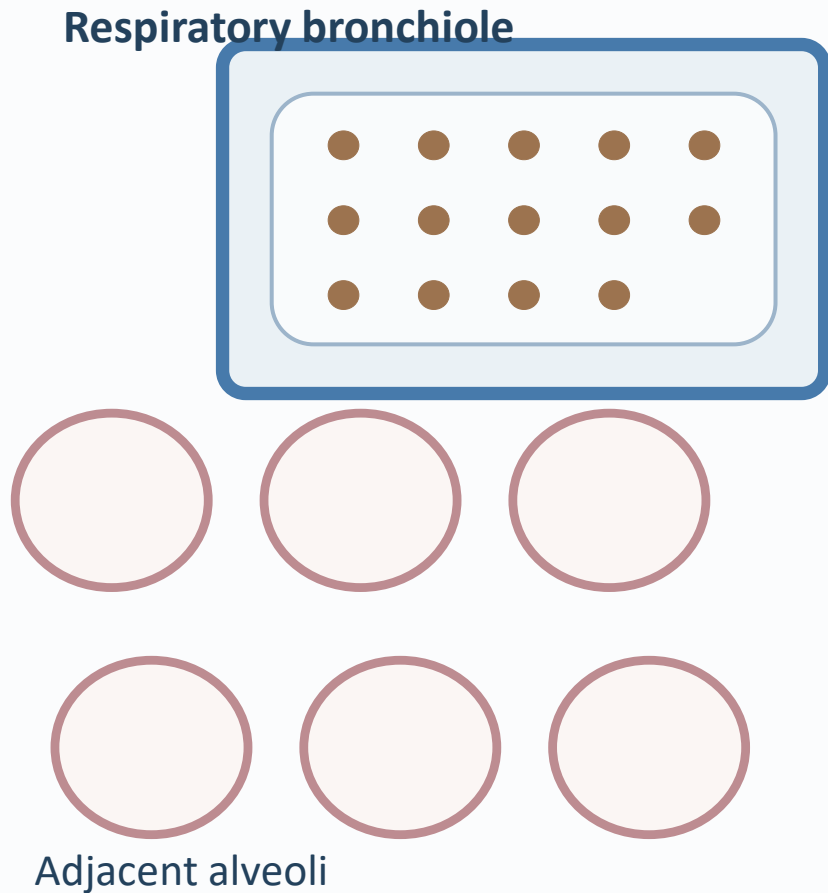
- Desquamative interstitial pneumonia (DIP)
- Respiratory bronchiolitis–associated ILD (RB-ILD)
- Inflammation and tissue remodeling

Smoking-related entities within diffuse interstitial lung disease



Classification is based on histologic distribution and clinical phenotype.

The respiratory acinus is the anatomic reference

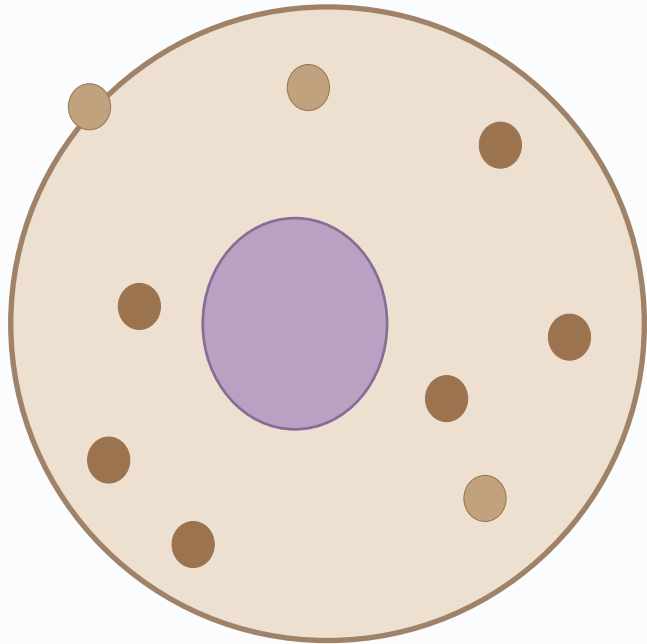


Simplified anatomic schematic — not histology

Why location matters

- Respiratory bronchioles lead toward alveolar ducts and sacs
- The dominant site of macrophages distinguishes these entities
- This schematic shows compartments, not a microscopic diagnosis

A common signature: The smoker's macrophage



Dusty brown cytoplasmic pigment

Simplified anatomic schematic — not histology

Shared finding

- Abundant cytoplasm with fine dusty brown pigment
- Found in DIP airspaces and RB respiratory bronchioles
- Pigment is descriptive, not by itself a named disease

Distribution matters more than macrophages alone

DIP: Alveolar emphasis

- Large airspace macrophage aggregates
- Alveolar septal reaction
- A predominantly intraalveolar pattern

RB-ILD: Bronchiolar emphasis

- Respiratory bronchioles and adjacent alveoli
- Patchy peribronchiolar changes
- Clinical disease required for the ILD label

Interstitial and obstructive findings can coexist

- DIP frequently accompanies emphysema and airway changes
- RB-ILD commonly accompanies mild centrilobular emphysema
- Coexisting obstructive morphology does not exclude an interstitial lesion

**Assess both
airway and
alveolar
compartments.**

Smoking and idiopathic pulmonary fibrosis: A caution

- Most patients with IPF are smokers
- The pathogenic role of smoking in IPF remains unclarified
- Association must not be presented as proof of causality

**Smoking
exposure ≠
established IPF
mechanism**

Two principal patterns are distinguished anatomically

Feature	DIP	RB-ILD
Dominant site	Alveolar airspaces	Respiratory bronchioles
Macrophages	Numerous, widespread	Bronchiolocentric, patchy
Septal reaction	Mild thickening/inflammation	Peribronchiolar inflammation/fibrosis
Clinical signature	Restrictive/diffusion abnormality	Smoking plus significant clinical impairment

DIP is an intraalveolar macrophage-rich process

Intraalveolar macrophage accumulation



Simplified anatomic schematic — not histology

Defining pattern

- Large numbers of macrophages fill alveolar spaces
- Patients are usually current or former smokers
- Fibrosis is absent or mild in most descriptions

Why “desquamative” is a historical misnomer

Original interpretation

Cells filling alveoli were
considered shed
pneumocytes



Current recognition

The predominant cells are
macrophages



Teaching implication

Do not interpret the label as
epithelial exfoliation

DIP distribution: Alveoli are the principal compartment

Intraalveolar macrophage accumulation

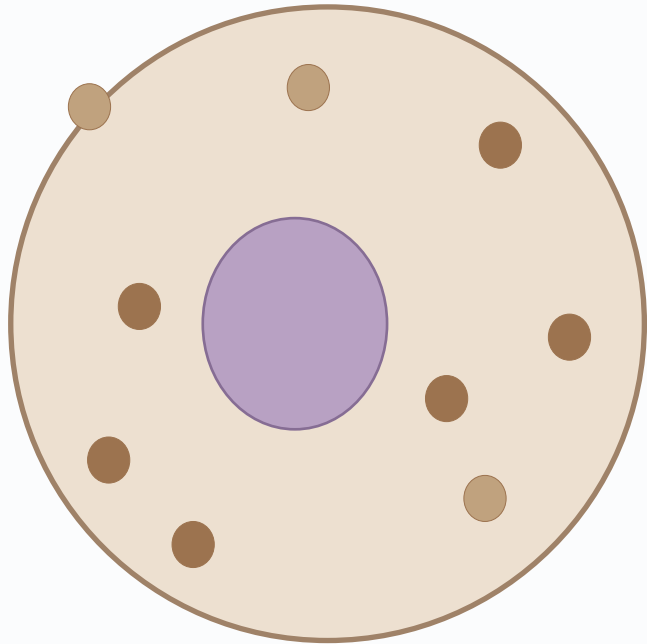


Simplified anatomic schematic — not histology

Location and architecture

- The diagnostic emphasis is on collections in airspaces
- Alveolar septa may be mildly thickened
- The finding is not centered on a single small airway

Smoker's macrophages in DIP: Abundant and pigmented



Dusty brown cytoplasmic pigment

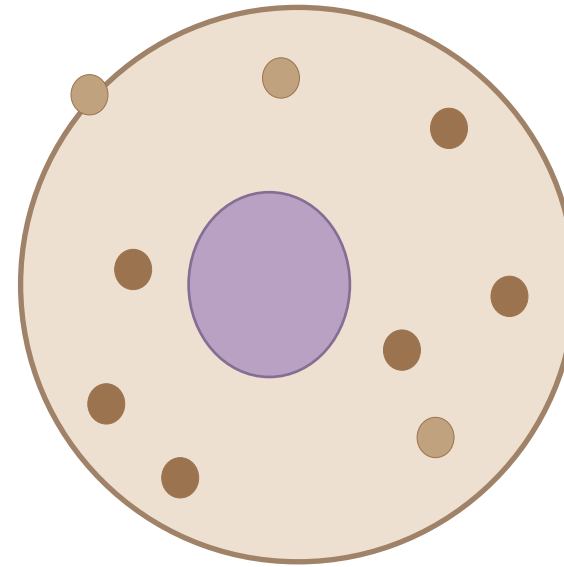
Simplified anatomic schematic — not histology

Cytologic profile

- Macrophages have voluminous cytoplasm
- The cytoplasmic pigment is dusty brown
- The aggregates dominate microscopic recognition

Dusty brown pigment is a shared histologic clue

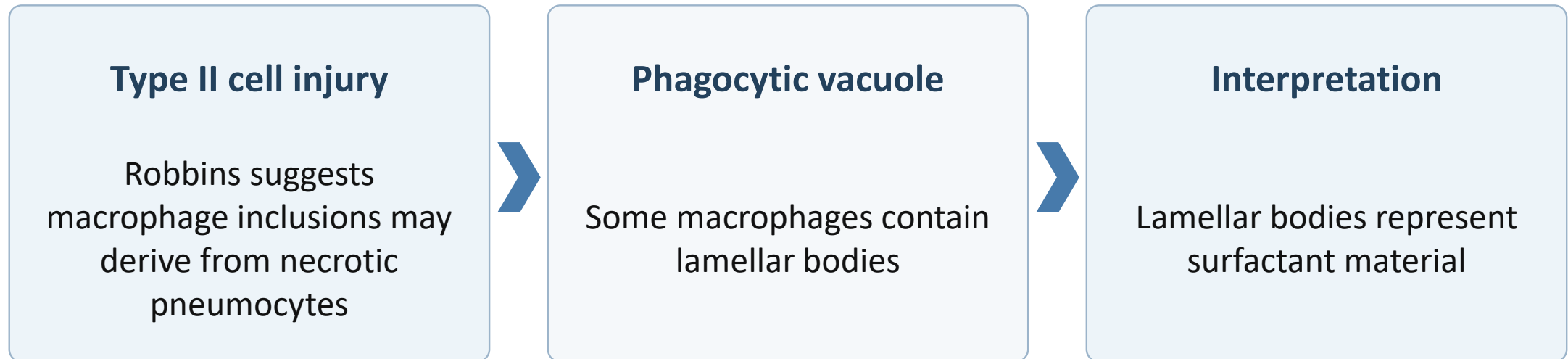
- Macrophage pigmentation supports a smoking-related phenotype
- DIP and RB-ILD share this macrophage appearance
- Their anatomic distributions distinguish the patterns



Shared cytology; Different location

Conceptual schematic

Surfactant lamellae may appear within DIP macrophages



The proposed source of the lamellar bodies is presumptive, not definitive.

DIP septa contain only a sparse inflammatory infiltrate

- Alveolar walls may be thickened by mild inflammation
- The infiltrate includes lymphocytes and plasma cells
- Occasional eosinophils also occur
- Macrophage-rich airspaces remain the dominant feature

**Airspace cells
predominate over
septal
inflammation.**

Cuboidal type II pneumocytes line affected alveoli

- Affected septa may be covered by plump cuboidal cells
- These represent type II pneumocyte changes described in DIP
- Do not mistake septal lining cells for the dominant luminal macrophages

**Distinguish lining
epithelium from
luminal
macrophages.**

Interstitial fibrosis in DIP is generally mild

- Septal fibrosis may be present but is usually limited
- DIP is not defined by dense destructive interstitial scarring
- Rare patients progress to interstitial fibrosis clinically

**Mild baseline
fibrosis ≠ zero
progression risk.**

Emphysema may coexist with DIP

DIP component

- Alveolar macrophage accumulation
- Mild septal thickening
- Mild restrictive functional defect

Associated smoking effects

- Emphysema
- Airway changes of obstructive disease
- Potential mixed morphologic phenotype

DIP morphology: Put the features together

Intraalveolar macrophage accumulation



Simplified anatomic schematic — not histology

Integrated H&E reading checklist

- Abundant intraalveolar macrophages
- Sparse septal inflammatory cells
- Cuboidal pneumocytes; Fibrosis usually mild
- Possible coexisting emphysema

Why DIP is not simply “fibrosis”

What dominates

- Macrophages occupy airspaces
- Pigmented abundant cytoplasm
- Alveolar rather than bronchiolar distribution

What accompanies

- Mild septal thickening
- Limited chronic inflammation
- Usually mild interstitial fibrosis

Typical DIP patient: Exposure and age

- Most patients are cigarette smokers
- Presentations typically occur in the fourth or fifth decade
- Comparable frequency in women and men

**Smoking history
has high
contextual value.**

DIP symptoms develop over weeks to months

Insidious onset

Symptoms develop gradually
over weeks or months



Primary symptoms

Dyspnea and dry cough



Associated sign

Digital clubbing occurs in
some patients

Digital clubbing can accompany DIP

- Clubbing as a common associated finding
- It should be interpreted alongside smoking exposure and respiratory symptoms
- Clubbing alone cannot establish DIP or identify anatomic distribution

**Clinical findings
require
morphologic
context.**

DIP typically produces a mild restrictive defect

- Pulmonary function testing often shows mild restriction
- This belongs to the broader restrictive/interstitial lung disease group
- Concurrent emphysema can complicate a simple obstructive/restrictive dichotomy

**The functional
signal is
commonly mild.**

Gas transfer is moderately reduced in typical DIP

- Diffusing capacity is often moderately decreased
- This adds functional evidence of parenchymal disease
- Interpret alongside pulmonary volumes and smoking-associated co-morbidity

**Reduction in
diffusion
supports a
pulmonary
process.**

DIP connects alveolar morphology with respiratory symptoms



This is clinicopathologic correlation—not a proven single-step mechanism.

Cessation and corticosteroids often improve DIP

Smoking cessation

- Central intervention in a smoking-associated disorder
- Associated with favorable course in typical cases
- Relevant to coexisting smoking-related lung changes

Steroid response

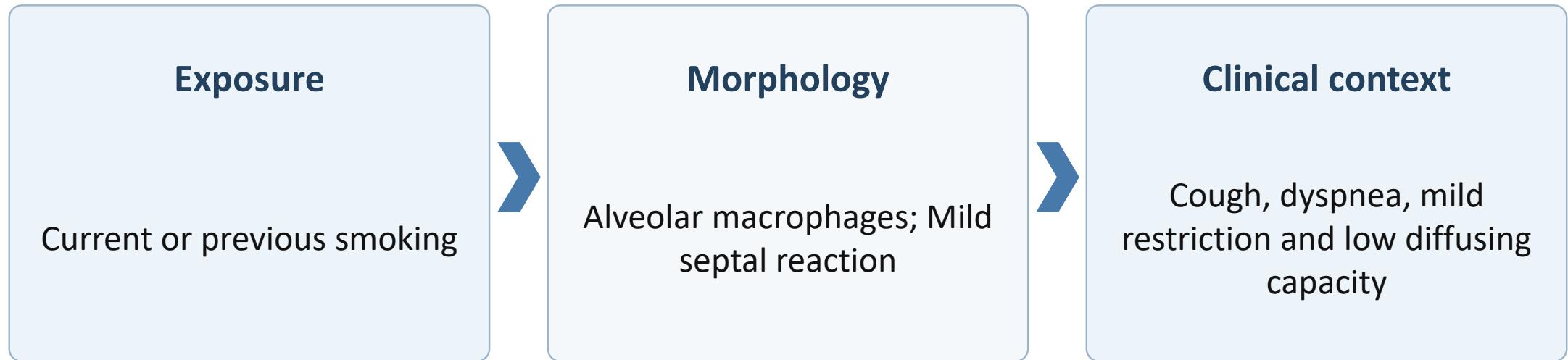
- Textbook describes an excellent typical response
- Outcome is not universally benign
- Treatment specifics are beyond this morphology-focused lecture

DIP prognosis: Favorable is not invariable

- An excellent usual treatment response
- Some patients nevertheless progress to interstitial fibrosis
- Assess the possibility of progression without exaggerating its frequency

“Usually responsive” does not mean “never progressive”.

DIP recognition: Integrate five domains

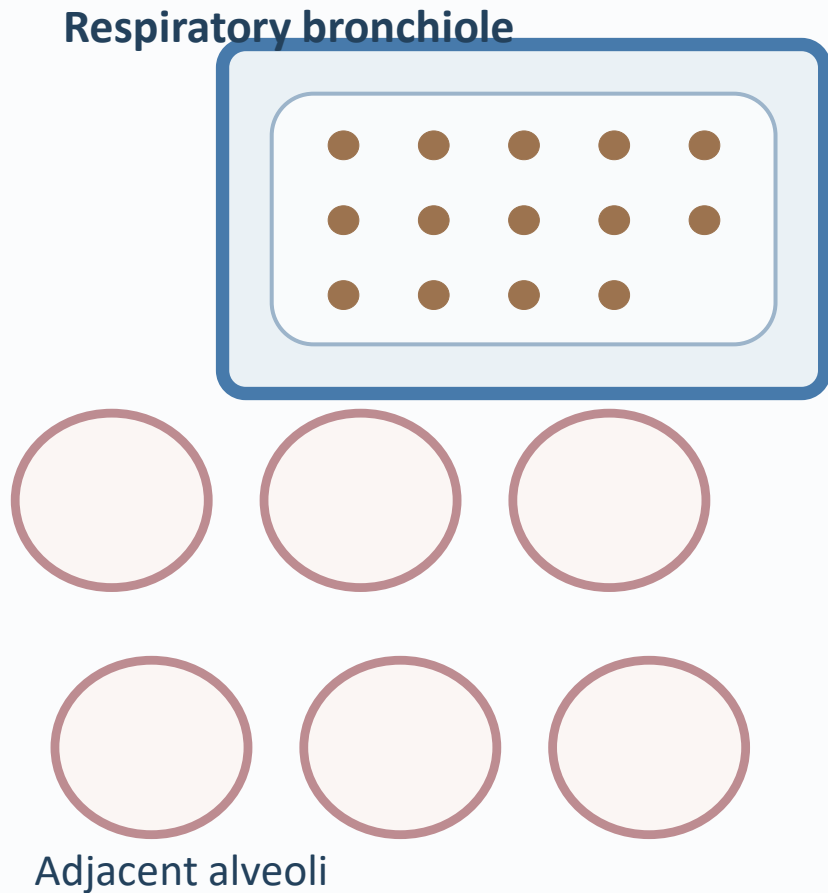


Respiratory bronchiolitis is common in smokers

- Pigmented intraluminal macrophages accumulate in respiratory bronchioles
- In mild form the finding can be incidental
- RB-ILD requires more than the histologic observation alone

**Lesion and
syndrome are not
synonymous.**

Respiratory bronchioles anchor the RB pattern

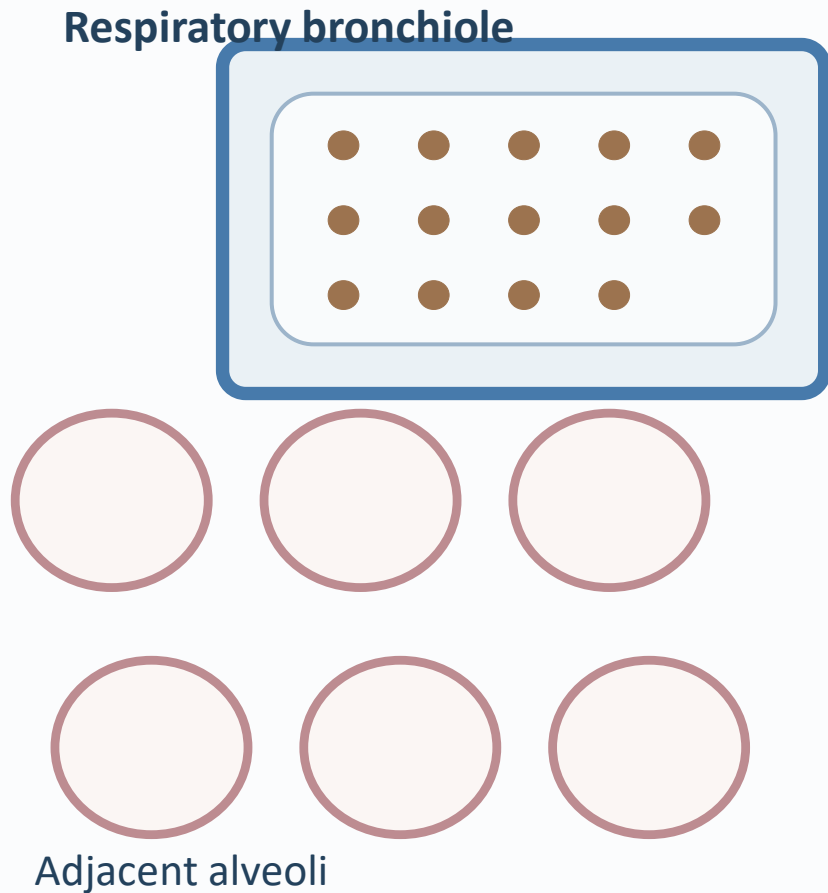


Simplified anatomic schematic — not histology

Anatomic location

- The emphasis is on first- and second-order respiratory bronchioles
- Adjacent alveolar ducts and peribronchiolar spaces may also be involved
- The overall pattern is bronchiolocentric

Smoking-related pigment occurs inside bronchioles



Simplified anatomic schematic — not histology

Pigment distribution

- Intraluminal smoker's macrophages are characteristic
- Pigment resembles that in DIP macrophages
- Macrophage localization gives the bronchiolocentric pattern

RB changes are patchy at low power

Low-power distribution

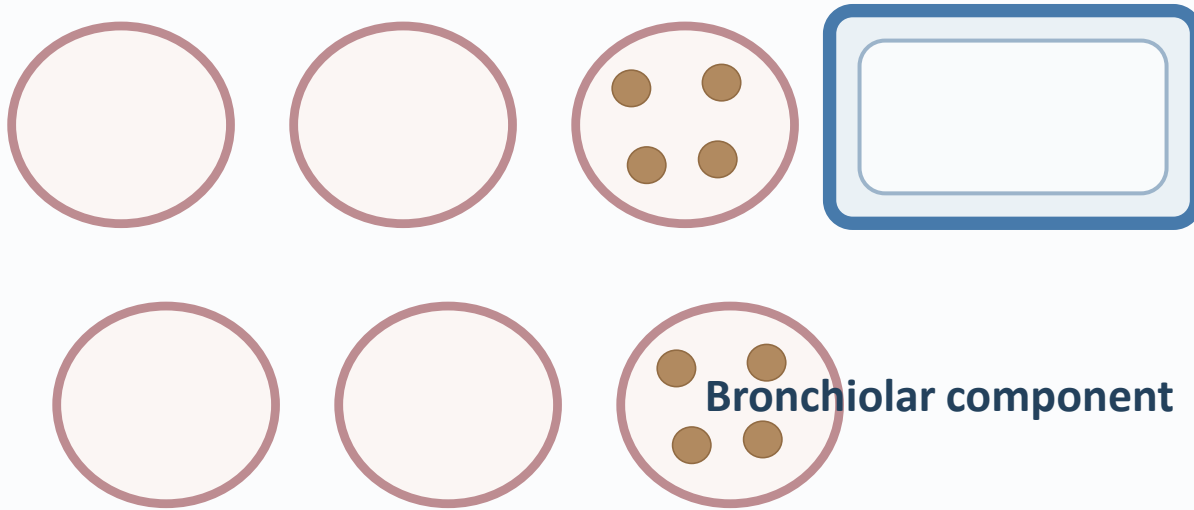
- Patchy rather than evenly diffuse
- Centered around small respiratory airways
- Different lung regions may show different lesion density

High-power clues

- Dusty brown macrophages
- Submucosal lymphocytes and histiocytes
- Mild fibrosis near bronchioles

Macrophages extend beyond the bronchiolar lumen

Alveolar macrophages



Bronchiolar component

Bronchiole → alveolar duct

- Respiratory bronchioles contain pigmented macrophages
- Alveolar ducts also may contain aggregates
- Peribronchiolar airspaces can contain the same cells

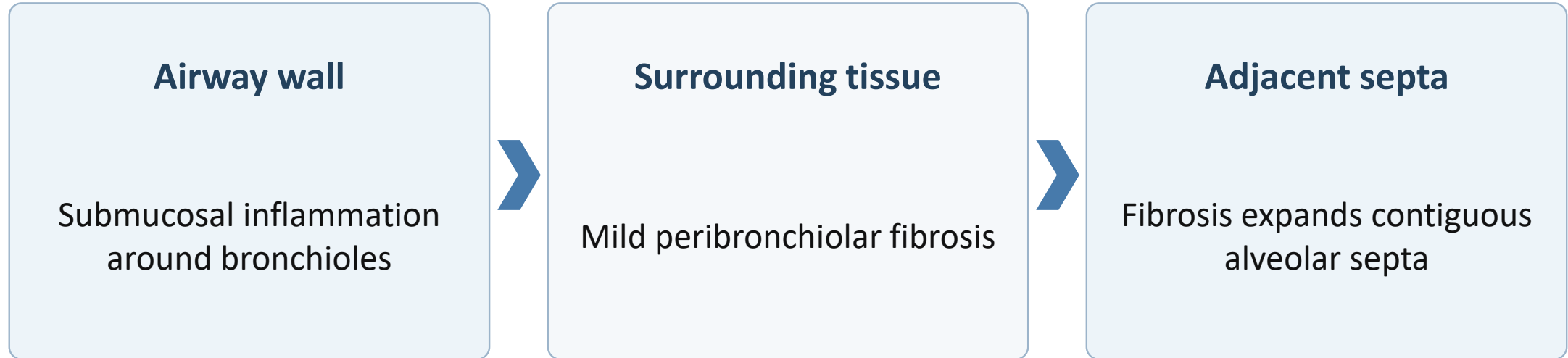
Simplified anatomic schematic — not histology

RB inflammation lies in the small-airway wall

- Patchy submucosal inflammation accompanies macrophages
- The infiltrate contains lymphocytes and histiocytes
- Inflammation extends into the peribronchiolar region

**Airway-centered
inflammation
supports RB
pattern.**

Peribronchiolar fibrosis extends into adjacent septa



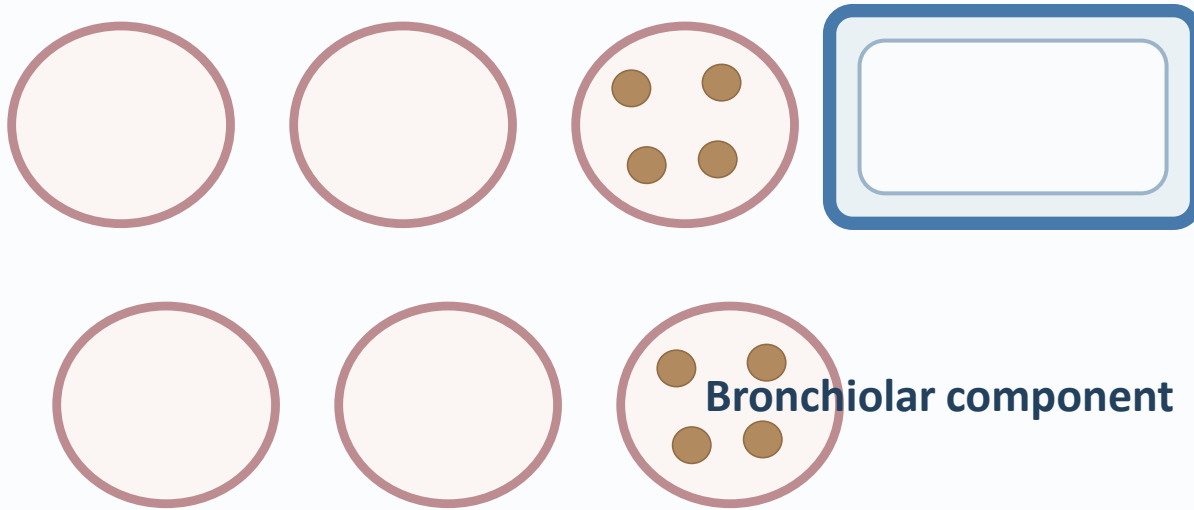
RB often coexists with centrilobular emphysema

- Centrilobular emphysema is common in the same specimens
- The emphysema is generally not severe description
- Coexistence emphasizes the wider effects of smoking on lung structure

**Do not overlook
accompanying
airway damage.**

DIP and respiratory bronchiolitis may coexist

Alveolar macrophages

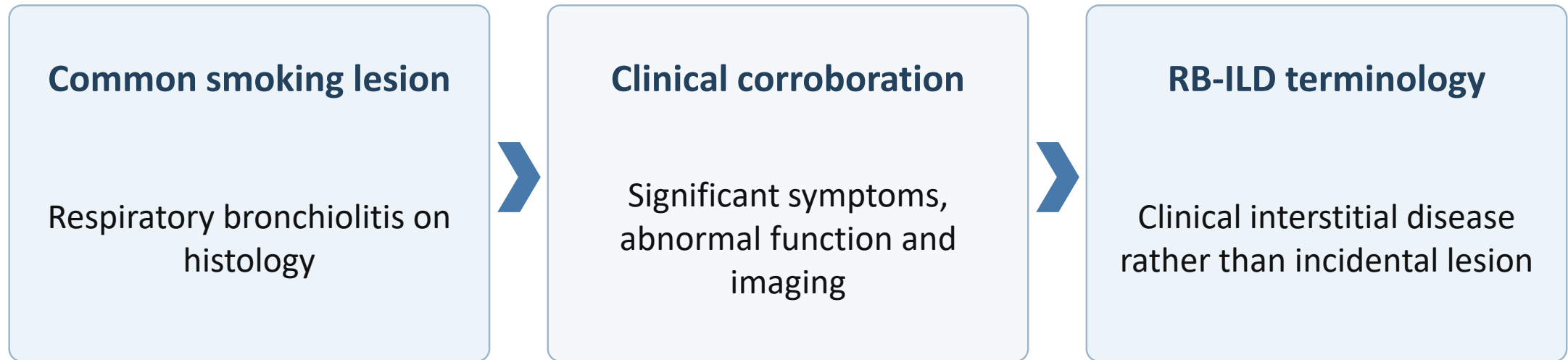


Simplified anatomic schematic — not histology

Regional heterogeneity

- The same lung may contain bronchiolocentric RB and DIP elsewhere
- One tissue sample does not necessarily represent every region
- Localize each pattern before applying a disease label

RB-ILD: Disease requires clinical significance



The diagnostic distinction is explicitly clinical, not only microscopic.

Typical RB-ILD patients have substantial exposure

- Patients are generally current smokers
- Exposures often exceeding 30 pack-years
- Presentation is typically in the fourth or fifth decade
- The exposure profile is contextual, not a standalone diagnostic threshold

**>30 pack-years is
typical, not a
required cutoff.**

RB-ILD symptoms are usually relatively mild

- Symptoms often develop gradually
- Cough and dyspnea predominate
- Clinical severity distinguishes RB-ILD from an incidental respiratory bronchiolitis lesion

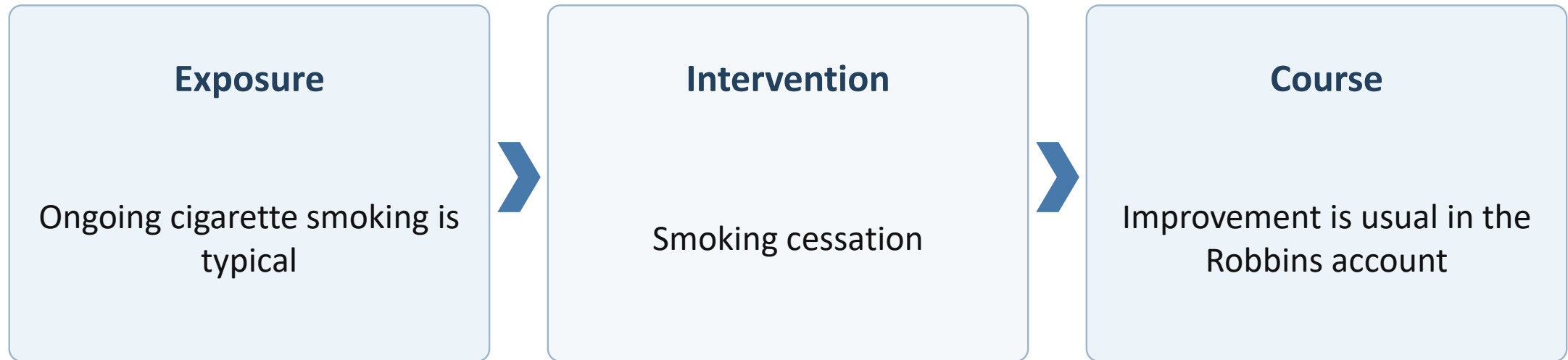
**Symptoms
determine clinical
relevance.**

Abnormal imaging and physiology support RB-ILD

- The disease label includes abnormal pulmonary function
- Imaging abnormalities are part of the definition
- The provided section does not specify a characteristic HRCT pattern
- Avoid inventing a diagnostic imaging cutoff

**Clinical evidence
is required;
Morphology
alone is
insufficient.**

Smoking cessation often improves RB-ILD



Do not infer a guaranteed or uniform response for every patient.

DIP versus RB-ILD: Dominant anatomic distribution

Parameter	DIP	RB-ILD
Center of lesion	Alveolar spaces	Respiratory bronchioles
Macrophages	Large intraalveolar collections	Small-airway and adjacent airspaces
Geographic pattern	Prominent alveolar involvement	Patchy, bronchiolocentric
Associated septa	Mild inflammatory thickening	Fibrosis adjacent to bronchioles
Emphysema	May coexist	Centrilobular form is common

DIP versus RB-ILD: Clinical distinctions

Parameter	DIP	RB-ILD
Exposure	Usually current/former smoker	Typically current heavy smoker
Symptoms	Dyspnea; Dry cough	Often mild dyspnea and cough
Function	Mild restriction, ↓ diffusion	Abnormality required for ILD label
Other clinical sign	Clubbing can occur	Not emphasized in source
Course	Cessation + steroids usually effective	Cessation usually improves

The same pigmented cells do not establish one disease

Features shared

- Smoker's macrophages
- Association with cigarette smoking
- Potential coexisting emphysema

Features discriminating

- Airspace-wide vs airway-centered localization
- Septal pattern and distribution
- Clinical lesion vs syndrome distinction

Beware of making smoking a universal explanation

- A smoking history is not sufficient to identify a specific ILD
- Robbins leaves smoking's pathogenetic role in IPF unresolved
- Mixed obstructive and interstitial findings may occur
- Morphology and clinical features must remain concordant

**Exposure
supports—but
does not
replace—
diagnosis.**

Pulmonary Langerhans cell histiocytosis is separate

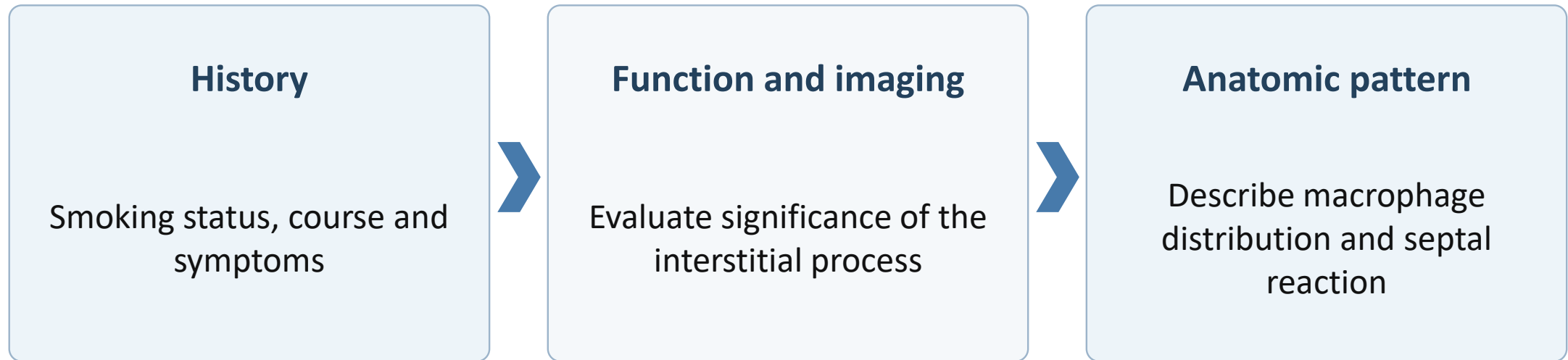
DIP / RB-ILD

- Pigmented macrophages dominate
- Alveolar or bronchiolocentric distributions
- Smoking-associated interstitial patterns

PLCH (adjacent topic)

- Langerhans cell aggregates, often with eosinophils
- Scarring and irregular cystic spaces
- Distinct nodular/cystic morphology

An integrated interpretation is preferable to one clue



A diagnosis must reconcile exposure, clinical disease and lung morphology.

Sampling can alter the apparent dominant pattern

- RB lesions are patchy and bronchiolocentric
- DIP may coexist in a different region of the same lung
- A sampled field may underrepresent regional heterogeneity
- Use the broader clinical picture and available tissue context

**Different regions
need not show
identical
morphology.**

Case 1: A DIP-type presentation

Teaching case (hypothetical)

A current smoker in the fifth decade develops several months of dry cough and exertional dyspnea. Function tests show mild restriction with reduced diffusing capacity. A teaching section depicts many macrophages filling alveolar spaces.

Question

Which smoking-related interstitial pattern is most strongly suggested—and what makes the distribution informative?

Case 1: Evidence supports DIP

- Intraalveolar macrophage accumulation is the dominant defining clue
- Insidious cough/dyspnea and mild restrictive impairment are compatible
- The reduced diffusing capacity supports clinical parenchymal involvement
- The histologic label still requires appropriate clinicopathologic correlation

Case 2: An incidental smoking lesion

Teaching case (hypothetical)

A smoker has dusty brown macrophages inside respiratory bronchioles in a specimen obtained for another indication. No pulmonary symptoms, physiologic impairment or reported imaging abnormality are present in the vignette.

Question

Does this finding alone justify the diagnosis of RB-ILD?

Case 2: Respiratory bronchiolitis $\neq$ RB-ILD

- Bronchiolar pigmented macrophages are common in smokers
- Respiratory bronchiolitis may be incidental
- RB-ILD requires clinically significant symptoms and abnormal function/imaging
- Do not promote a common histologic lesion to a clinical disease automatically

Case 3: When RB becomes clinically significant

Teaching case (hypothetical)

A current smoker with substantial cumulative exposure develops slowly progressive cough and dyspnea. Physiologic testing and imaging are abnormal. Tissue shows patchy bronchiolocentric smoker's macrophages and mild peribronchiolar fibrosis.

Question

Which findings support the RB-ILD designation rather than incidental RB?

Case 3: Clinical and pathologic concordance

- Bronchiolocentric macrophages establish an RB-type lesion
- The symptoms, abnormal physiology and imaging meet the clinical threshold
- Mild peribronchiolar fibrosis fits the source morphology
- Cessation of smoking is associated with typical improvement

Clinicopathologic synthesis

Question	Evidence favoring DIP	Evidence favoring RB-ILD
Where?	Alveolar airspaces	Small respiratory bronchioles
Which cells?	Numerous smoker's macrophages	Pigmented bronchiolar macrophages
What tissue response?	Mild septal inflammation	Mild peribronchiolar fibrosis
What clinical role?	Symptomatic interstitial process	Significant RB-associated clinical disease

Five defensible conclusions

- DIP and RB-ILD are smoking-associated but anatomically distinct
- Both contain dusty brown smoker's macrophages
- DIP primarily fills alveoli; RB lesions center on respiratory bronchioles
- RB-ILD requires demonstrable clinical disease
- Smoking cessation is central; DIP may respond to steroids

**Location + clinical
significance
determine
interpretation.**

Primary source and boundaries

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 15, “The Lung,” p. 637: Smoking-Related Interstitial Diseases.

Parent context: Chronic Diffuse Interstitial (Restrictive) Diseases, pp. 627–628; relevant classification and physiologic framework.

Adjacent differential boundary: Pulmonary Langerhans Cell Histiocytosis, p. 637. Original schematic drawings are conceptual; no diagnostic photomicrographs are reproduced.