

Invasion of Extracellular Matrix

How carcinomas cross tissue barriers, reshape their microenvironment, and acquire motility

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Learning objectives

- Identify the successive extracellular barriers encountered by an invasive carcinoma.
- Explain the four interdependent steps of extracellular matrix invasion.
- Relate E-cadherin, proteases, integrins, and actin-based motility to invasive behavior.
- Interpret stromal cooperation and the transition to intravasation.

Local invasion and distant metastasis are distinct

Local invasion

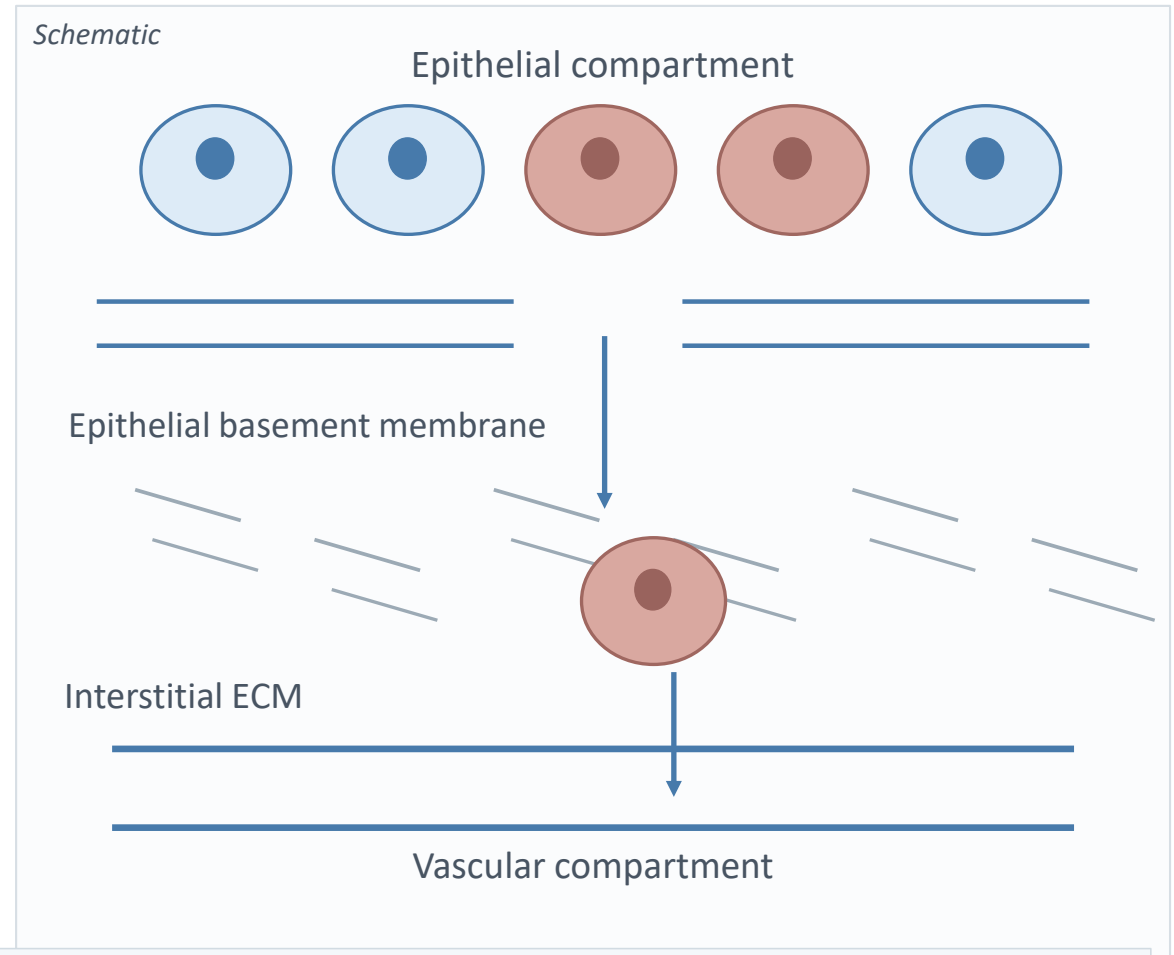
- Direct penetration of adjacent tissue compartments
- Requires altered adhesion, ECM remodeling, and motility
- Can destroy structures at the primary site

Distant metastasis

- Requires additional vascular dissemination and colonization
- Only a minority of entering tumor cells form deposits
- Depends on interactions with distant host environments

Invasion is an active cellular program

- Carcinoma cells do not simply expand through a pre-existing opening.
- They alter contacts with neighboring cells and extracellular matrix.
- Proteolysis, receptor engagement, and movement are coordinated with stromal responses.



A breached boundary requires tumor-cell behavior—not growth alone.

Two extracellular matrix compartments

Basement membrane

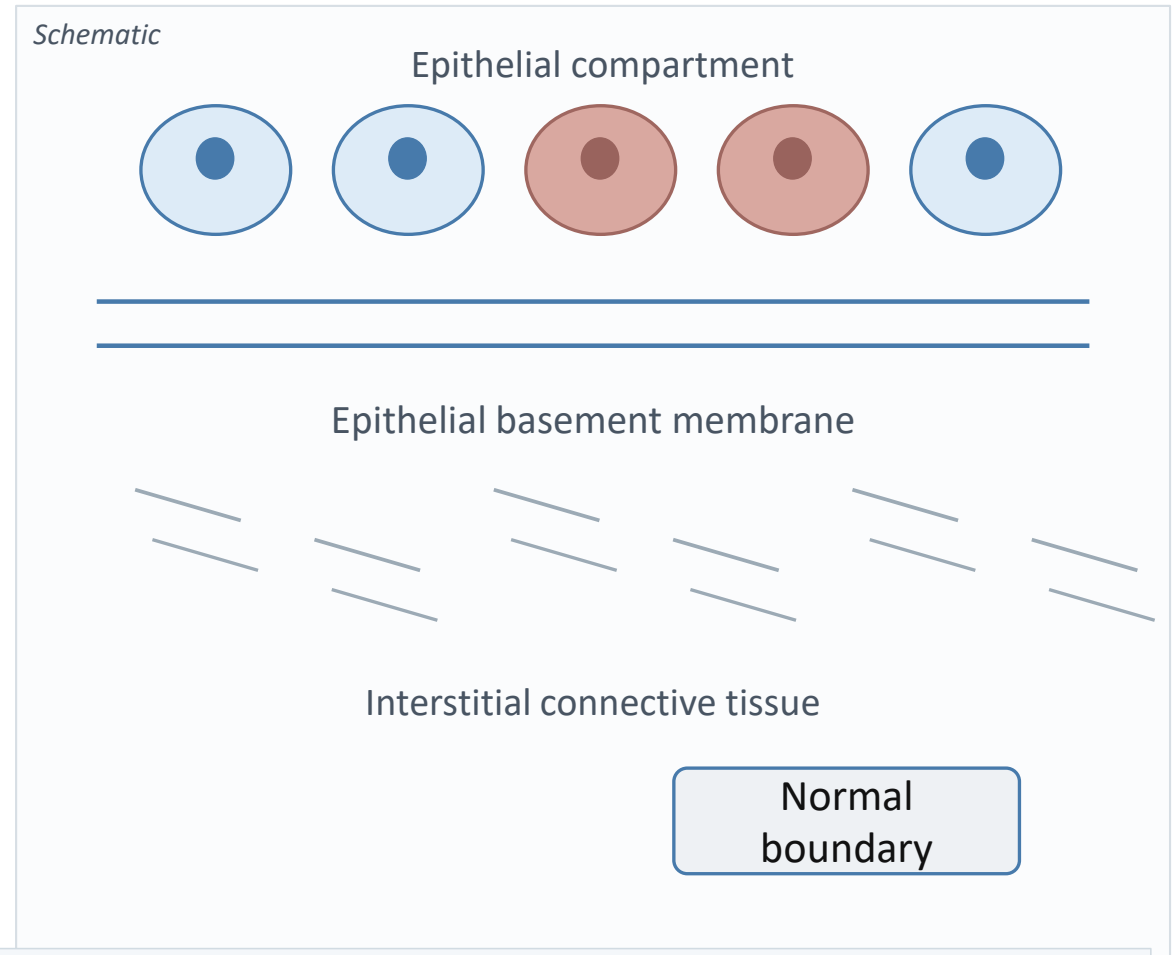
- Separates epithelial and vascular compartments from adjacent tissue
- Contains type IV collagen and laminin
- An early and later barrier to disseminating cells

Interstitial connective tissue

- Lies between epithelial structures and blood vessels
- Includes collagens, glycoproteins, and proteoglycans
- Must be crossed during movement toward a vessel

The epithelial basement membrane defines a boundary

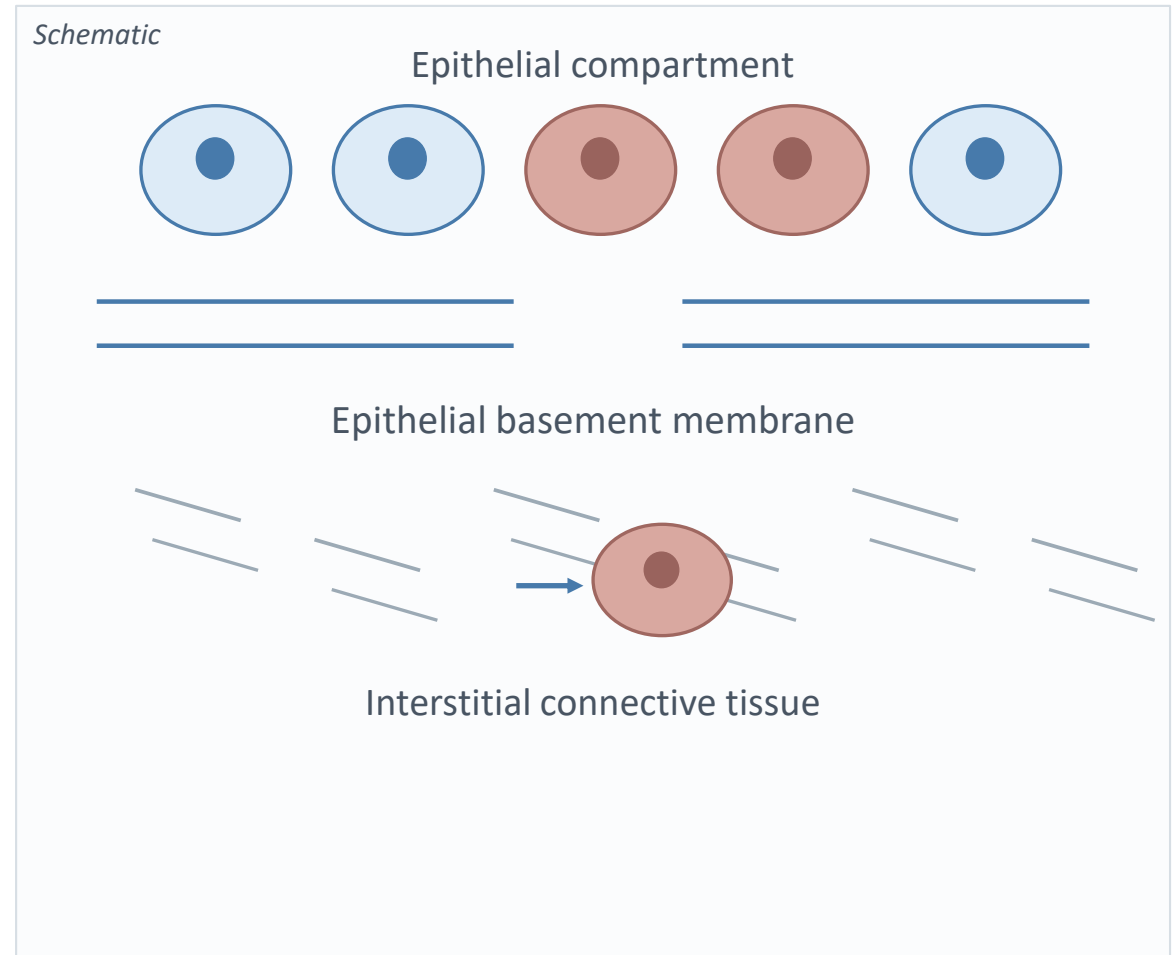
- The basement membrane separates epithelial cells from the underlying connective tissue.
- Carcinoma invasion requires penetration of this barrier.
- Matrix organization also shapes cell attachment, signaling, and polarity.



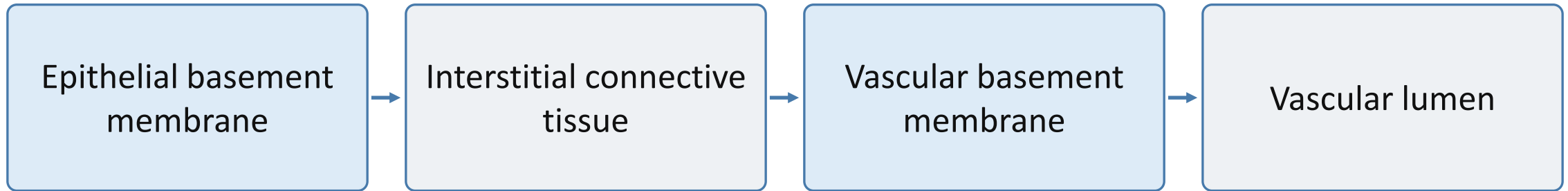
Crossing an epithelial basement membrane is a topologic change.

Interstitial matrix is more than empty space

- Connective tissue matrix occupies the path between an epithelial tumor and its vascular access.
- Its constituents provide both physical resistance and binding sites for cells.
- Matrix cleavage creates a route and biologically active fragments.



The route from epithelium to circulation



In a distant organ, exiting the vessel requires barrier traversal in reverse.

Matrix components have structural and signaling roles

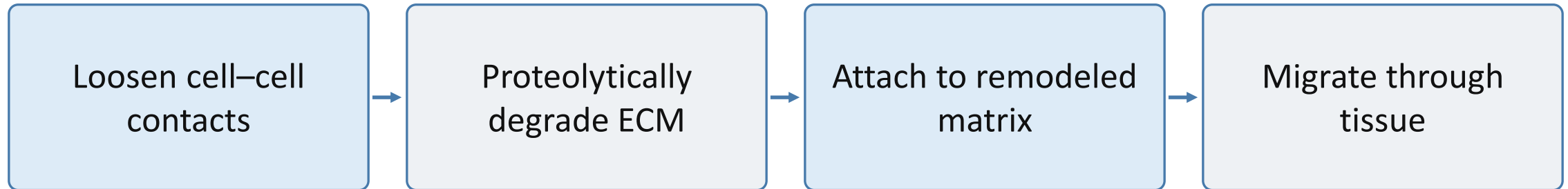
Structural barrier

- Type IV collagen supports basement membranes
- Interstitial matrix maintains tissue compartmentation
- Continuity limits unrestrained tissue traversal

Biologic interface

- Laminin and collagen serve as receptor ligands
- Proteolysis uncovers additional binding sites
- Stored growth factors can be released by degradation

Four linked steps drive local invasion

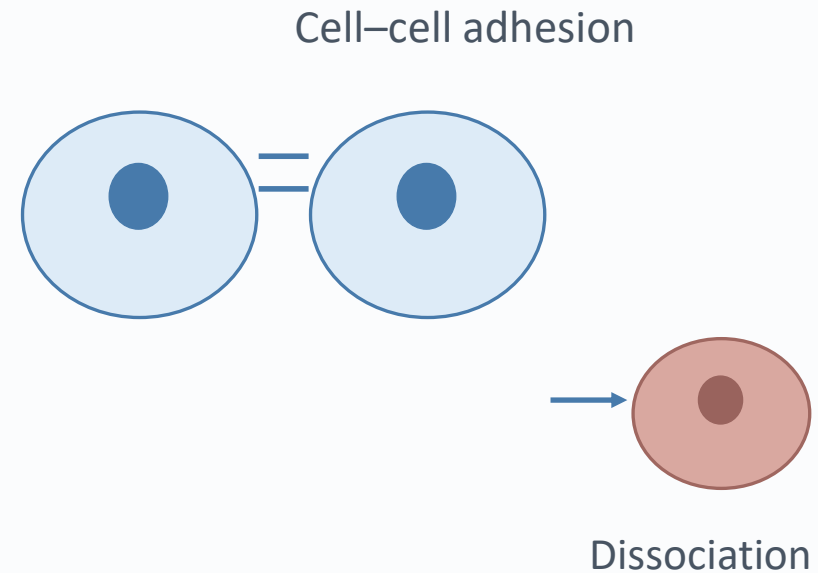


The steps cooperate; The diagram is a teaching sequence, not four isolated switches.

Adhesion loss enables tumor-cell detachment

- Normal epithelial cells maintain strong cell–cell junctions.
- Altered intercellular adhesion can dissociate tumor cells from one another.
- This is the initiating step in the Robbins four-step model of invasion.

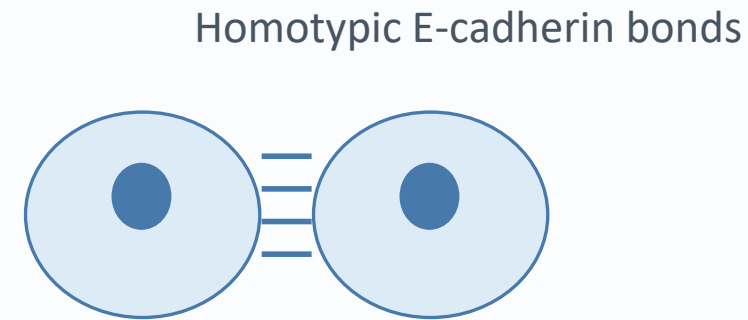
Schematic



E-cadherin mediates homotypic epithelial adhesion

- E-cadherin is a transmembrane glycoprotein expressed by epithelial cells.
- Its interactions help preserve cohesion between cells of the same epithelial compartment.
- Disruption of its function weakens the contacts that restrain dissociation.

Schematic

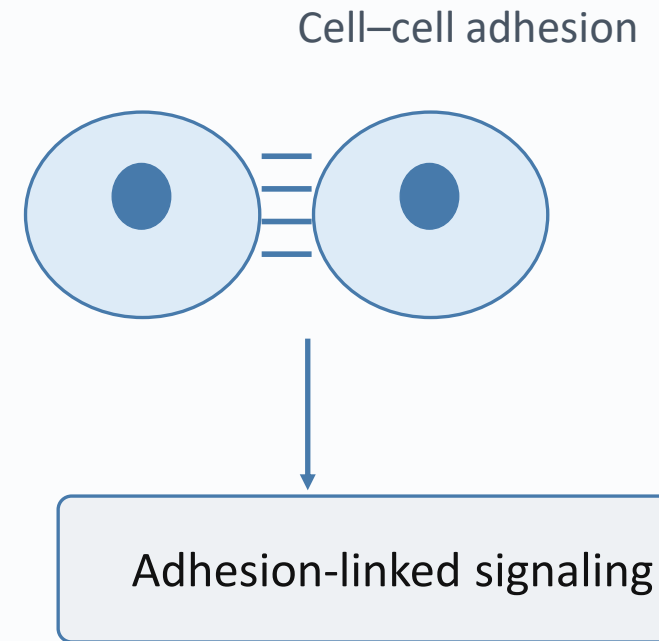


Cohesive epithelium

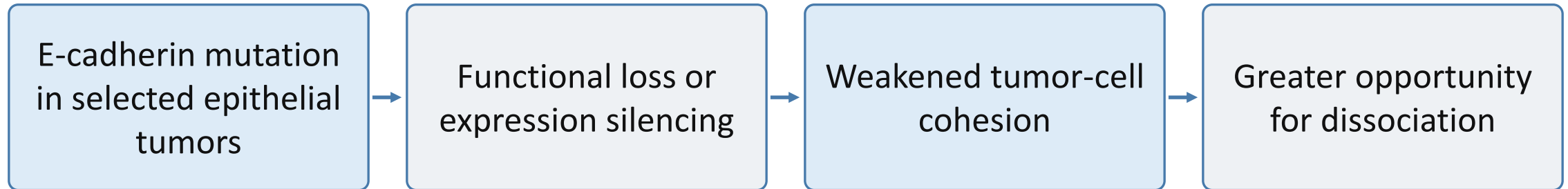
E-cadherin also transmits intercellular signals

- E-cadherin participates in signaling as well as physical adhesion.
- Loss of function affects coordinated epithelial behavior, not only mechanical cohesion.
- Adhesion molecules therefore connect tissue architecture to cell phenotype.

Schematic



Two paths to impaired E-cadherin function

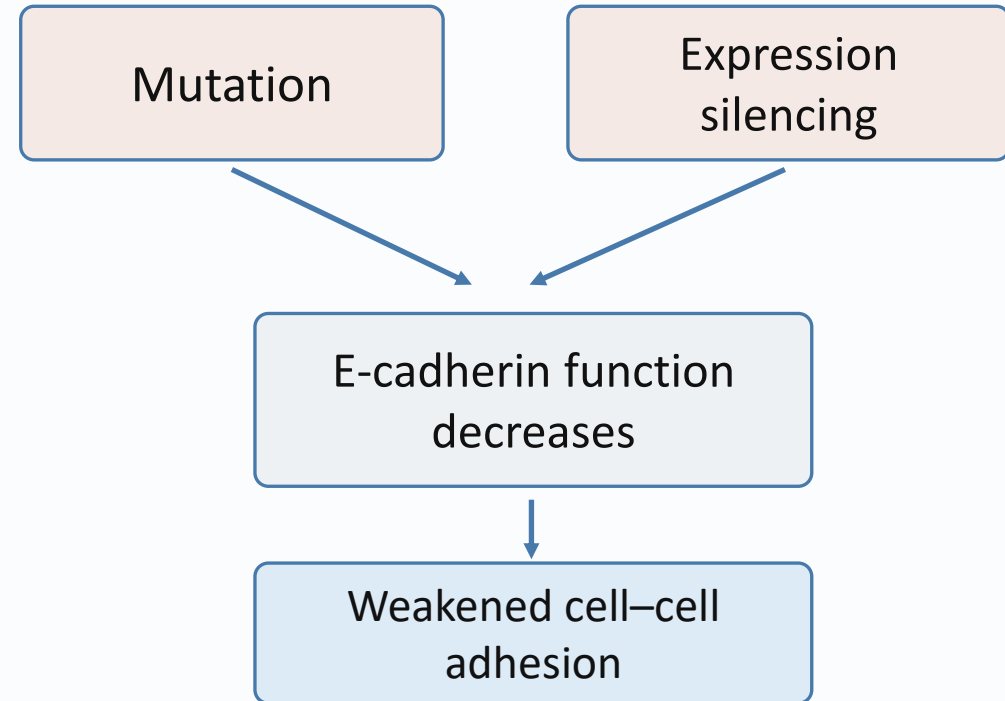


The source describes both genetic loss and hypothesized, sometimes transient, silencing.

Loss-of-function mutations are tumor-specific examples

- Certain gastric and breast adenocarcinomas with E-cadherin loss due to mutation.
- This is not presented as a universal mechanism in every carcinoma.
- Many other epithelial cancers may reduce E-cadherin through different regulatory routes.

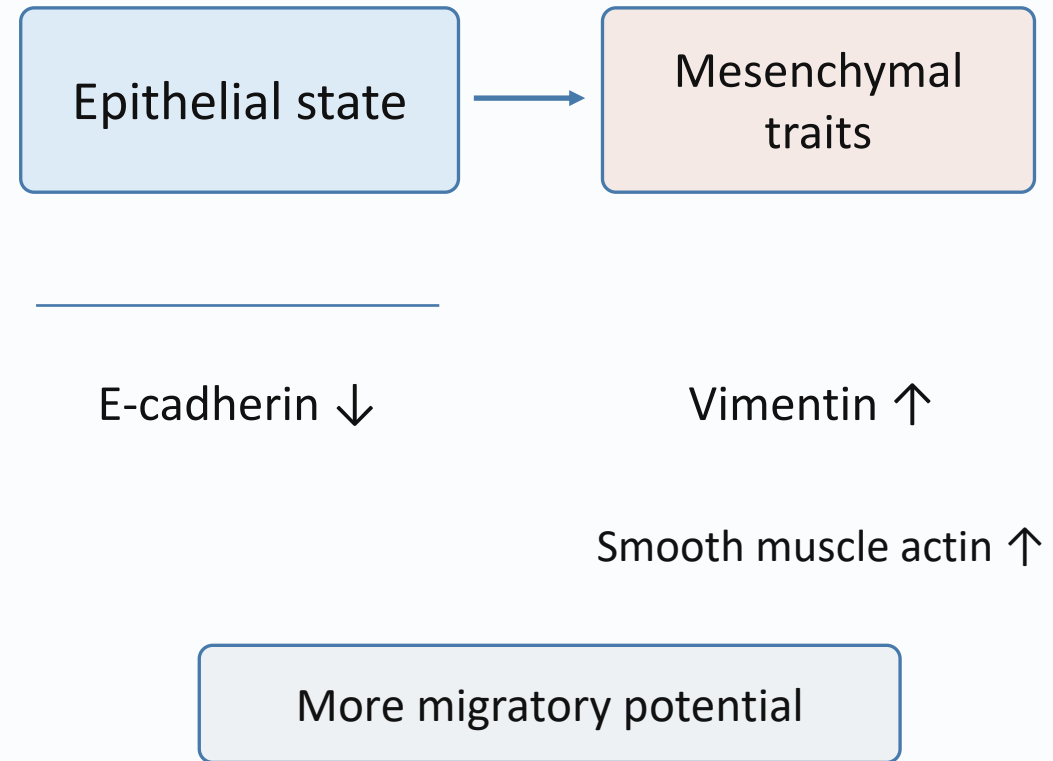
Schematic



Epithelial–mesenchymal transition is a proposed route

- Epithelial–mesenchymal transition (EMT) changes epithelial-marker expression and motility-associated traits.
- That EMT contributes to carcinoma invasion and metastasis.
- Its role is expressed as a hypothesis, not an invariant requirement for all metastases.

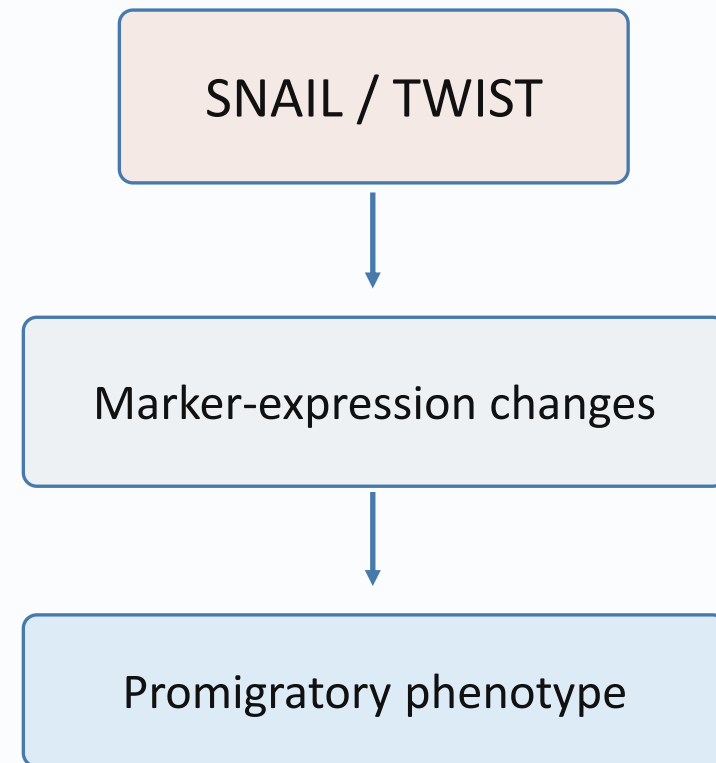
Schematic



SNAIL and TWIST participate in EMT regulation

- The transcription factors SNAIL and TWIST are named regulators of the EMT program.
- Their activity is linked to altered epithelial and mesenchymal marker expression.
- The phenotypic consequence is thought to favor a migratory carcinoma cell.

Schematic



EMT changes a coordinated marker pattern

Epithelial-associated

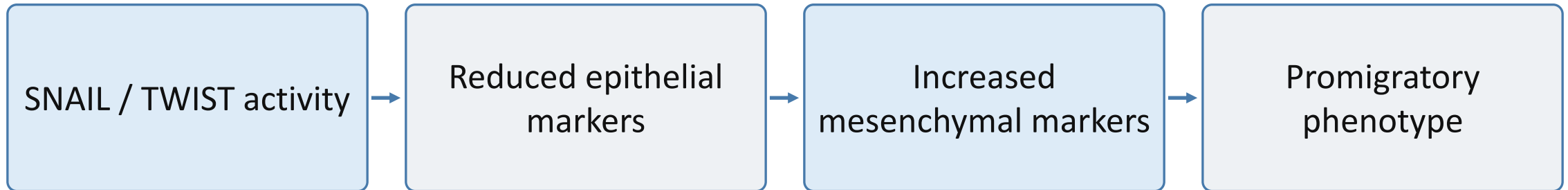
- E-cadherin expression
- Cohesive cell–cell interactions
- Maintained epithelial organization

Mesenchymal-associated

- Vimentin expression
- Smooth muscle actin expression
- Promigratory traits

Markers describe a coordinated phenotype; No single marker establishes metastatic behavior.

EMT links transcription to cellular behavior

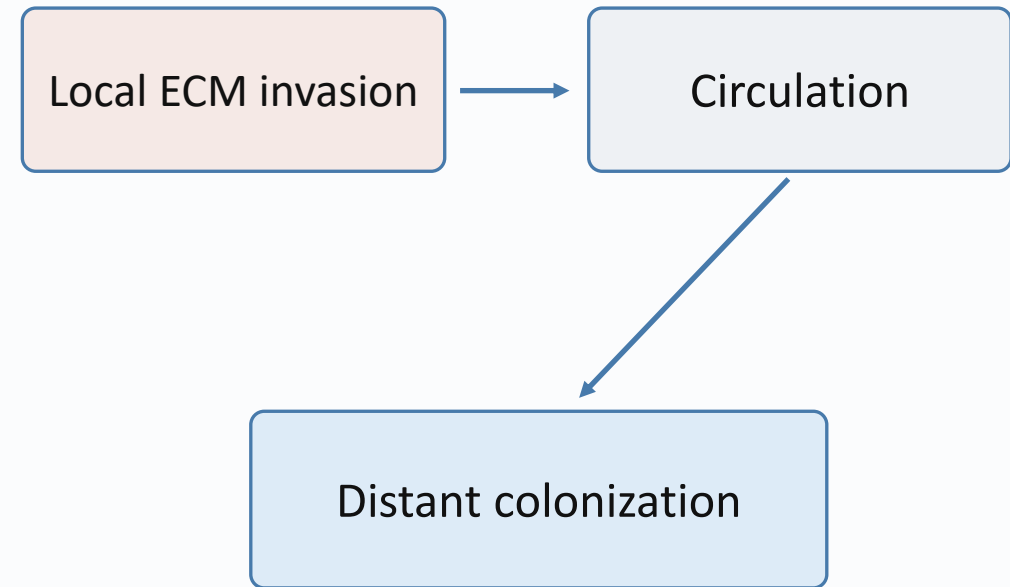


The causal framing follows the hypothesized mechanism.

EMT is not identical to successful metastasis

- Enhanced motility helps local tissue invasion but does not guarantee distant colonization.
- The metastatic cascade also requires circulation, survival, homing, and growth.
- Different tumor-cell phenotypes and even cohesive groups may participate.

Schematic



Separate later steps

Adhesion changes create an invasive opportunity

A carcinoma retains proliferation but shows reduced intercellular cohesion. Which invasion step is directly facilitated?

Mechanistic interpretation

- The first step: Loosening tumor cell–tumor cell interactions.
- Reduced cohesion alone does not demonstrate ECM proteolysis or migration.
- Additional processes are required to breach the basement membrane.

ECM degradation removes physical obstacles

- Proteolysis acts on epithelial basement membrane and interstitial connective tissue.
- Breaches in matrix permit tumor cells to enter neighboring tissue compartments.
- The same principle applies when approaching a vascular basement membrane.

Schematic

Extracellular matrix barrier



Tumor / stromal proteases

Matrix breach / remodeled ECM

Proteases originate from tumor cells and stroma

Tumor-cell contribution

- Secretion of matrix-degrading proteases
- Signals that induce protease release from stroma
- Participation in remodeling at the invasion front

Stromal contribution

- Fibroblasts can produce proteases
- Inflammatory cells can produce proteases
- The tumor microenvironment participates actively

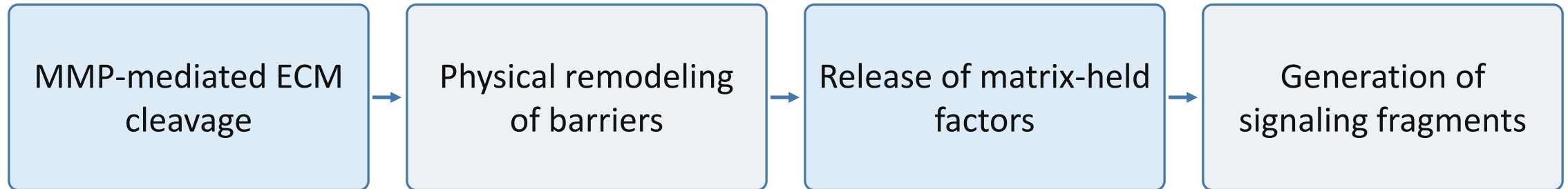
Three protease systems highlighted by Robbins

Matrix metalloproteinases Remodel basement membrane and interstitial matrix

Cathepsin D A protease implicated in tumor-cell invasion

Urokinase plasminogen activator A proteolytic system implicated in tumor-cell invasion

Matrix metalloproteinases do more than digest



Proteolysis is simultaneously structural remodeling and biologic signaling.

MMP9 acts on type IV collagen

- MMP9 is described as a gelatinase that cleaves type IV collagen.
- Type IV collagen is present in epithelial and vascular basement membranes.
- This action supports penetration of basement-membrane barriers.

Schematic

Type IV collagen (basement membrane)



MMP9

Matrix breach / remodeled ECM

Epithelial and vascular basement membranes share vulnerability

At the primary epithelium

- Basement-membrane cleavage permits invasion into stroma
- Loss of compartment boundary enables local tissue infiltration

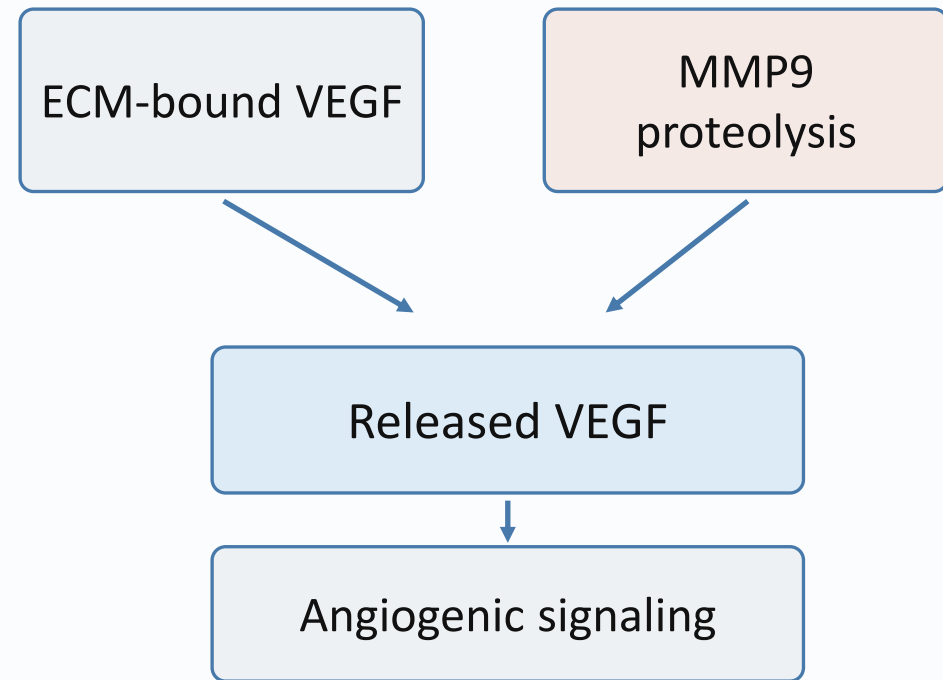
At the vessel

- Vascular basement-membrane remodeling assists entry
- Subsequent endothelial transmigration gives vascular access

MMP9 can mobilize matrix-sequestered VEGF

- ECM can retain vascular endothelial growth factor (VEGF).
- MMP9-mediated release of VEGF from these stores.
- Thus matrix degradation can contribute to an angiogenic microenvironment.

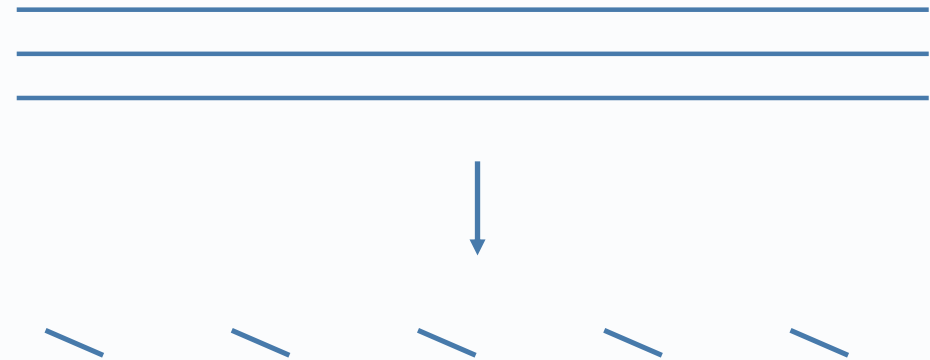
Schematic



ECM cleavage products can act as signals

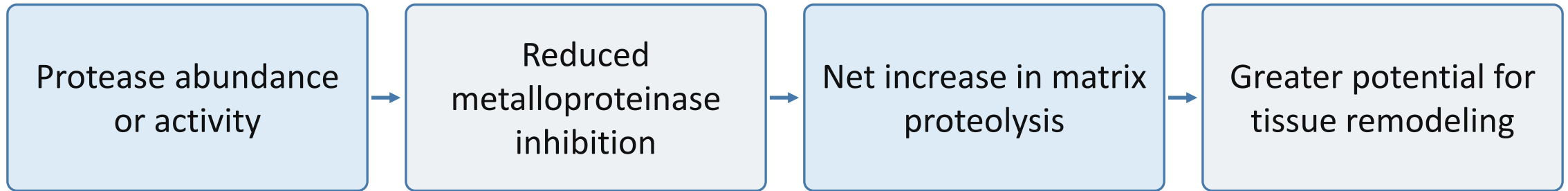
- Cleavage of collagen and proteoglycans yields matrix-derived fragments.
- Some products with chemotactic, angiogenic, and growth-promoting effects.
- Degradation products can therefore influence subsequent cell behavior.

Schematic



Chemotactic / angiogenic / growth effects

Protease activity reflects a balance



A greater net proteolytic drive favors invasion; The model is qualitative.

Reduced inhibitors reinforce ECM degradation

- Several cancers show decreased concentrations of metalloproteinase inhibitors.
- Lower inhibition shifts the local balance toward proteolysis.
- Invasion depends on the functional protease–inhibitor relationship, not a single enzyme in isolation.

Schematic

Protease activity

Inhibitor activity

Net ECM degradation reflects the balance

More degradation when proteolysis predominates

MMP9 differs qualitatively by tumor behavior

Benign tumors

- Little MMP9 activity in benign breast, colon, and stomach tumors.
- This is a qualitative tissue comparison.

Malignant counterparts

- The corresponding malignant tumors may overexpress MMP9.
- The text provides no numerical test cutoff.

Do not infer a stand-alone diagnostic MMP9 threshold from this comparison.

Proteolysis and motility must cooperate

Suppose matrix breakdown is extensive, but tumor cells cannot form new ECM attachments. What step remains impaired?

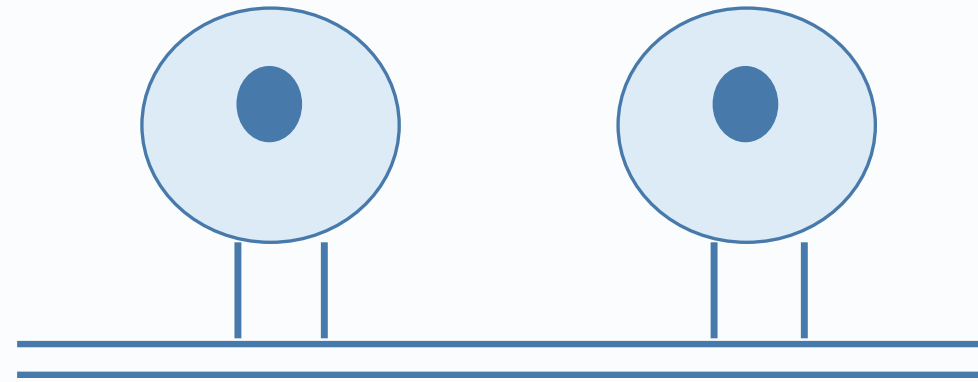
Mechanistic interpretation

- Attachment to remodeled ECM components is still deficient.
- Proteolysis alone does not provide traction for locomotion.
- The sequence requires coordinated receptor binding and actin-based movement.

Integrins link tumor cells to extracellular matrix

- Integrins are transmembrane receptors that bind components of ECM.
- They mediate adhesion and transmit intracellular signals.
- Changes in integrin expression or localization alter tumor–matrix interactions.

Schematic



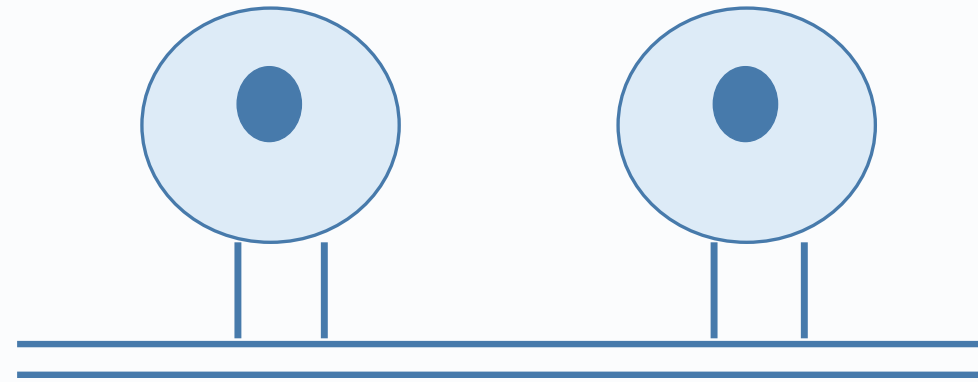
Integrin–ECM interactions

Receptors transmit matrix-derived signals

Normal epithelial integrins are basally restricted

- Basal integrins bind basement-membrane laminin and collagens.
- Their polarized distribution supports the resting state of epithelial cells.
- Loss of normal polarity is part of altered neoplastic cell–matrix interaction.

Schematic



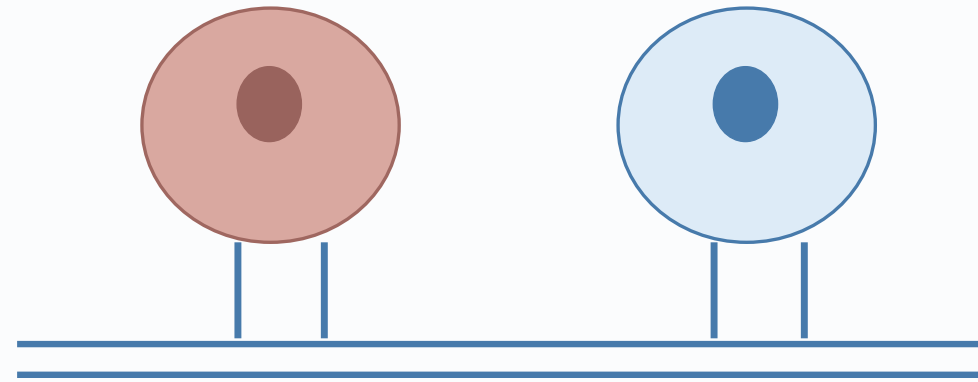
Basal receptor polarity

Attachment supports epithelial polarity

Cancer cells alter the integrin repertoire

- Complex changes in integrin expression during invasion.
- Alternative integrins can support attachment under abnormal ECM conditions.
- Some integrin signals also promote survival when normal adhesion is lost.

Schematic



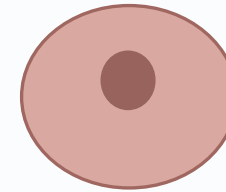
Altered integrin engagement

Different receptors can support survival

Normal detached cells may undergo anoikis

- Normal epithelial cells depend on appropriate ECM attachment.
- Loss of adhesion can trigger a form of apoptosis termed anoikis.
- Anoikis helps distinguish normal attachment dependence from free tumor-cell survival.

Schematic



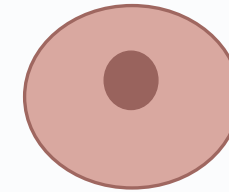
Detached epithelial cell

Anoikis (apoptosis)

Anoikis resistance favors invasive survival

- Tumor cells may survive despite losing their customary matrix contacts.
- This in part to alternative integrins delivering survival signals.
- Resisting anoikis is useful as cells detach and traverse changing ECM niches.

Schematic



Detached epithelial cell



Alternative integrin survival
signals

MMP2 and MMP9 expose new attachment sites

- MMP2 or MMP9 cleavage can modify type IV collagen and laminin.
- Proteolysis creates novel sites that tumor-cell receptors can bind.
- The newly available contacts may stimulate cell migration.

Schematic



MMP2 / MMP9 cleavage

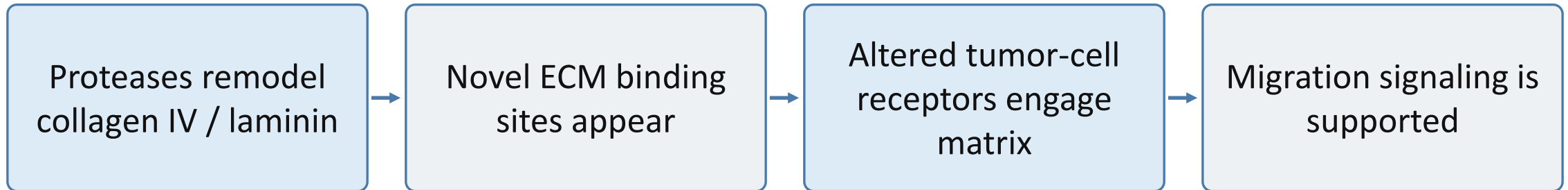


Novel ligand sites



Tumor receptor binding

Degradation and receptor binding reinforce one another



The matrix becomes an active migration substrate after remodeling.

ECM serves as both barrier and migratory track

Before remodeling

- Intact architecture separates tissue compartments
- Polarized attachment supports epithelial organization

After remodeling

- Proteolysis opens passages and exposes ligands
- Tumor cells can attach to altered matrix and move

Why detachment alone is insufficient

A cell loses E-cadherin but remains sensitive to anoikis. What limits its invasive fitness?

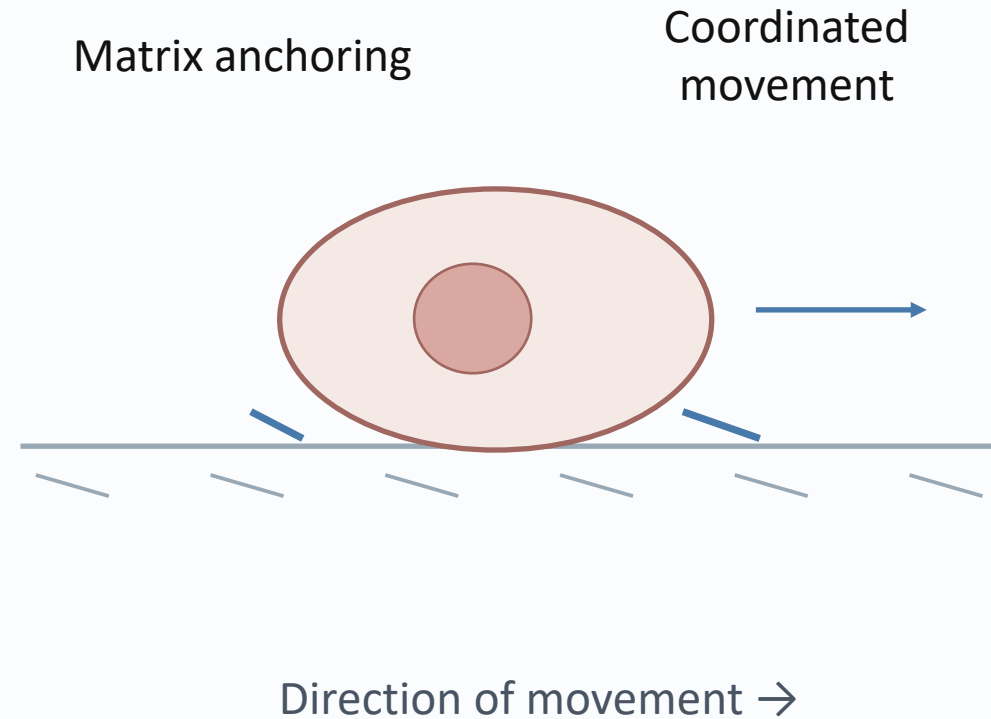
Mechanistic interpretation

- Cell–cell dissociation may occur, but ECM detachment can still trigger apoptosis.
- Resistance to anoikis provides a survival advantage under altered attachment.
- Adhesion, survival, and movement are separate requirements.

Locomotion closes the four-step invasion sequence

- The final step is tumor-cell movement through regions of matrix breakdown.
- Movement requires receptor signals and the actin cytoskeleton.
- Adhesion must be dynamically assembled and disassembled.

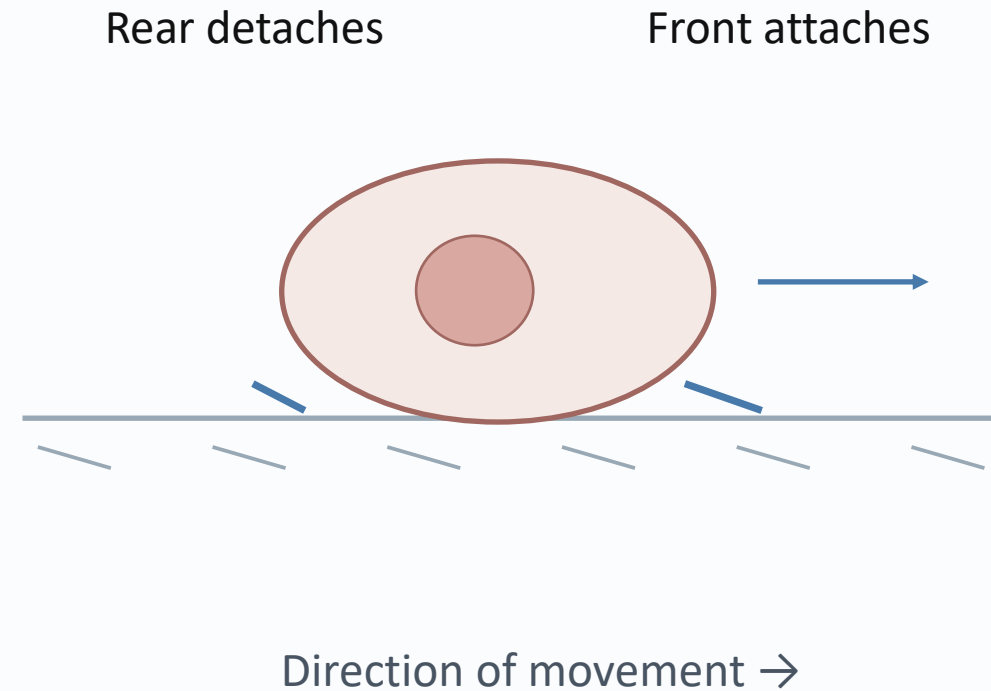
Schematic



The migrating cell has a front and a rear

- The leading edge creates new attachments to matrix.
- The trailing edge releases previous attachments.
- Actin-based contractility enables net displacement through tissue.

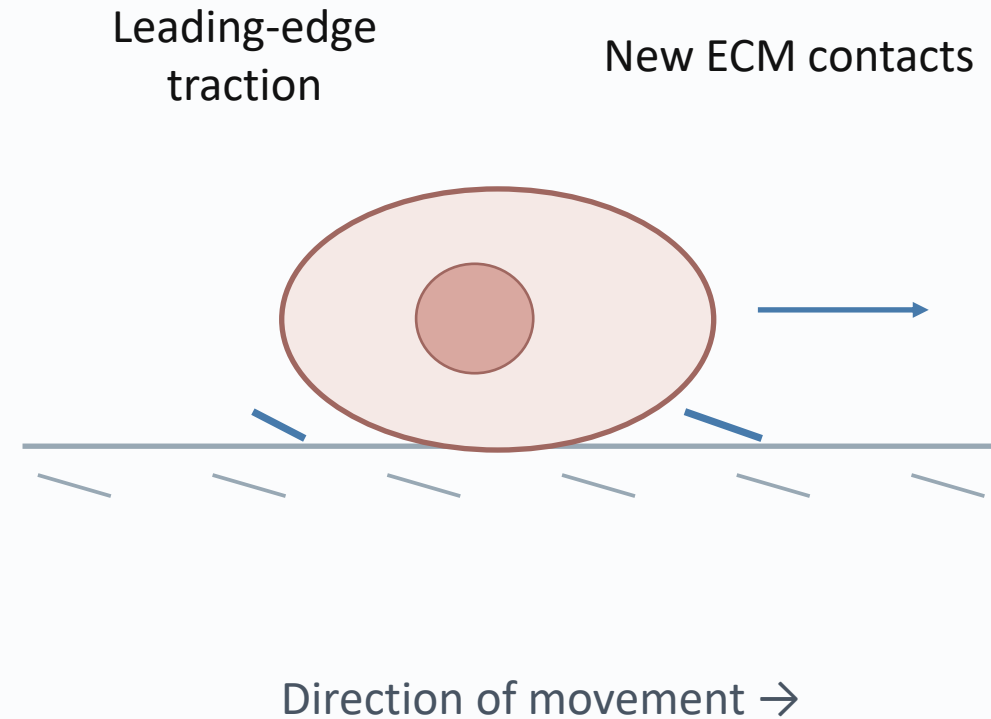
Schematic



Leading-edge adhesion provides traction

- A migrating tumor cell must bind the matrix ahead of its body.
- Receptor engagement anchors the leading edge during movement.
- Remodeled ECM provides potential sites for these new attachments.

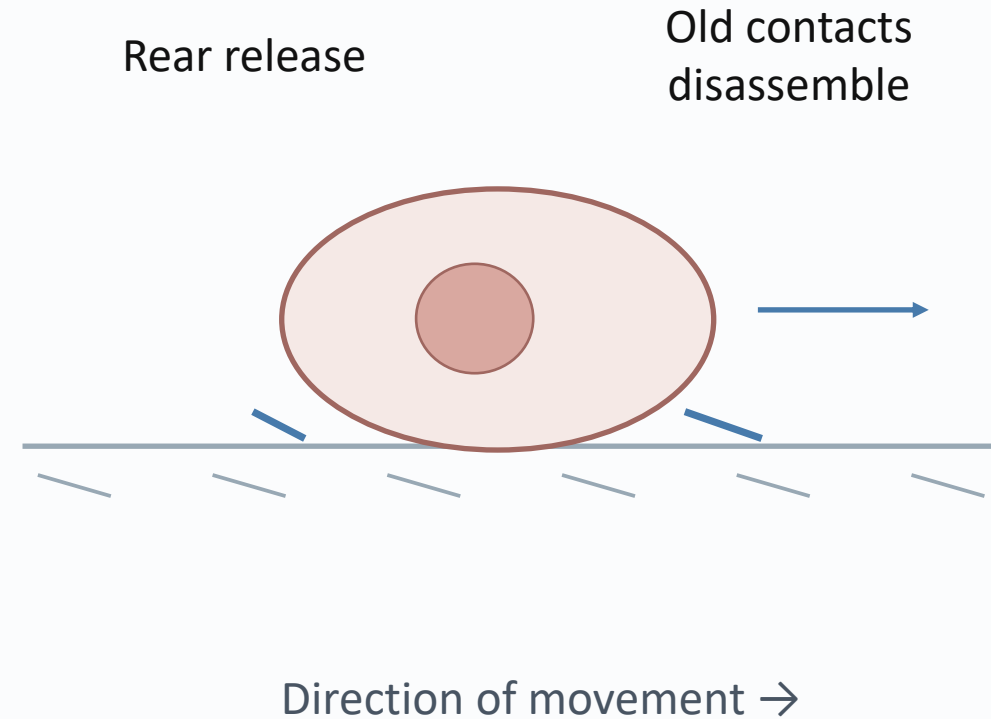
Schematic



Trailing-edge release allows forward movement

- Persistent adhesion at the cell rear would oppose net translation.
- Migrating cells therefore detach matrix contacts at their trailing edge.
- Turnover of cell–matrix contacts is as important as their formation.

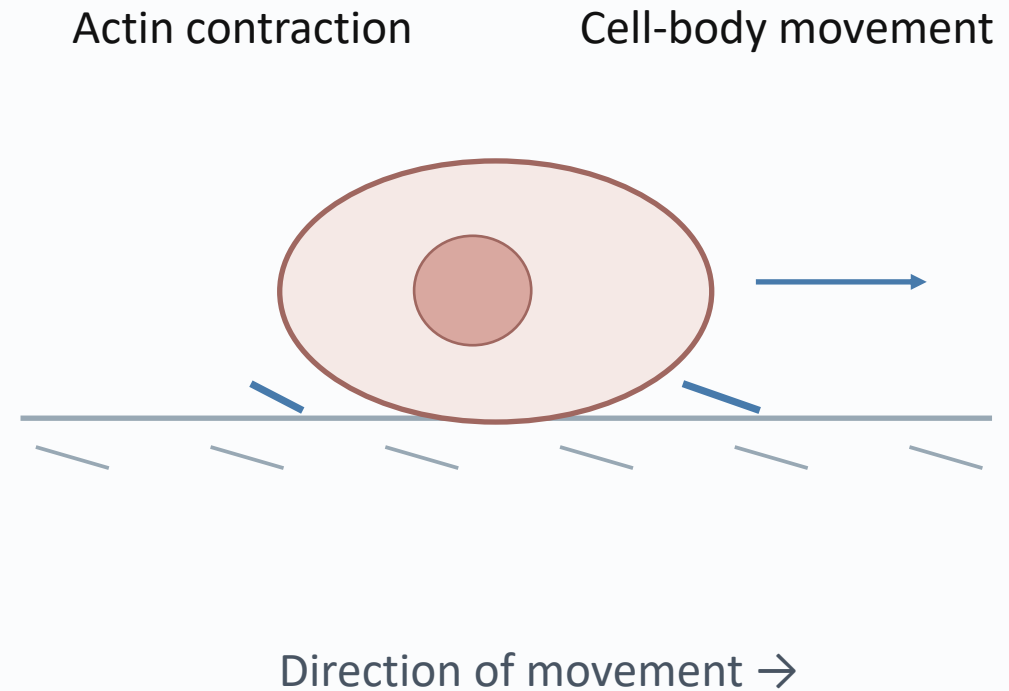
Schematic



Actin contraction generates cell translocation

- Multiple signaling pathways converge on the actin cytoskeleton.
- Contractile movement can draw the cell body forward relative to anchored contacts.
- Migration depends on spatial coordination, not simply stronger adhesion.

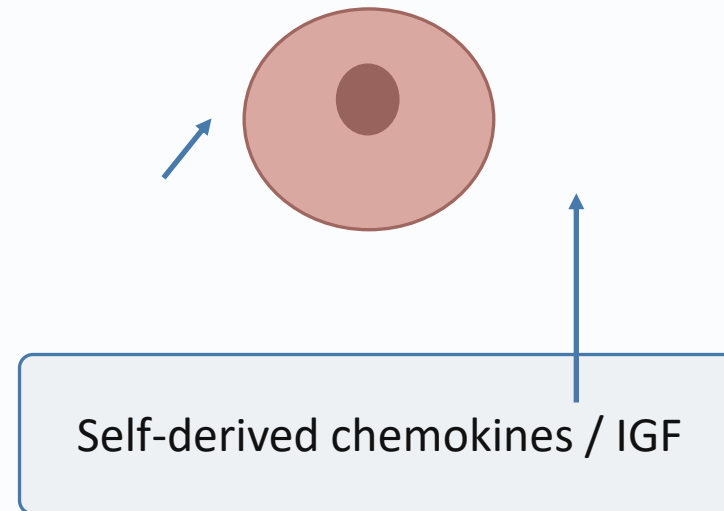
Schematic



Motility cues can be autocrine

- Tumor cells can produce cytokines and chemokines that affect their own movement.
- Robbins also cites growth factors, including insulin-like growth factors.
- Such self-derived signals are described as autocrine motility factors.

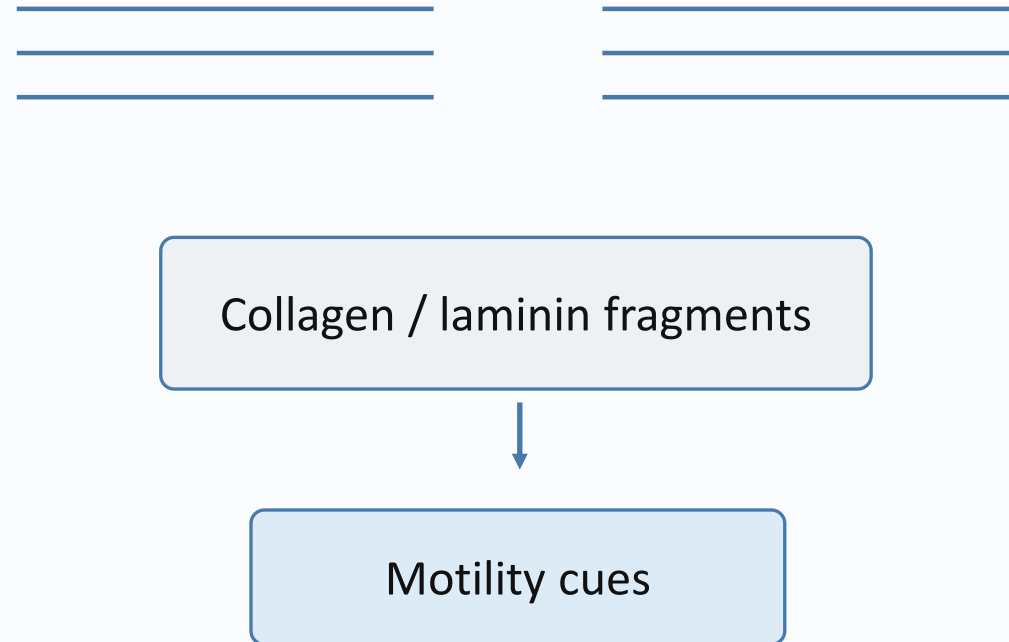
Schematic



Matrix cleavage products provide another cue

- Degradation of collagen or laminin can release biologically active fragments.
- These matrix-derived products may influence tumor-cell movement.
- Thus the physical path and the local guidance environment change together.

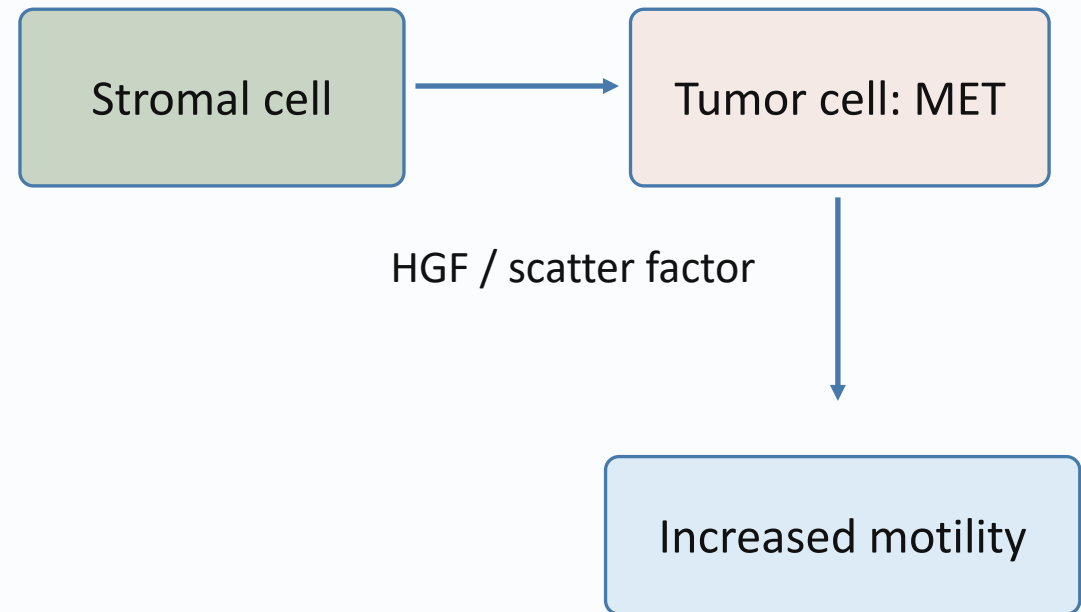
Schematic



Stromal HGF stimulates tumor-cell MET

- Stromal hepatocyte growth factor (HGF), also called scatter factor, is a paracrine cue.
- HGF binds MET, a receptor tyrosine kinase on tumor cells.
- This pathway as promoting tumor-cell motility.

Schematic



Three sources of directional/motility signals

Tumor-derived

- Chemokines and cytokines
- Insulin-like growth factors
- Autocrine stimulation

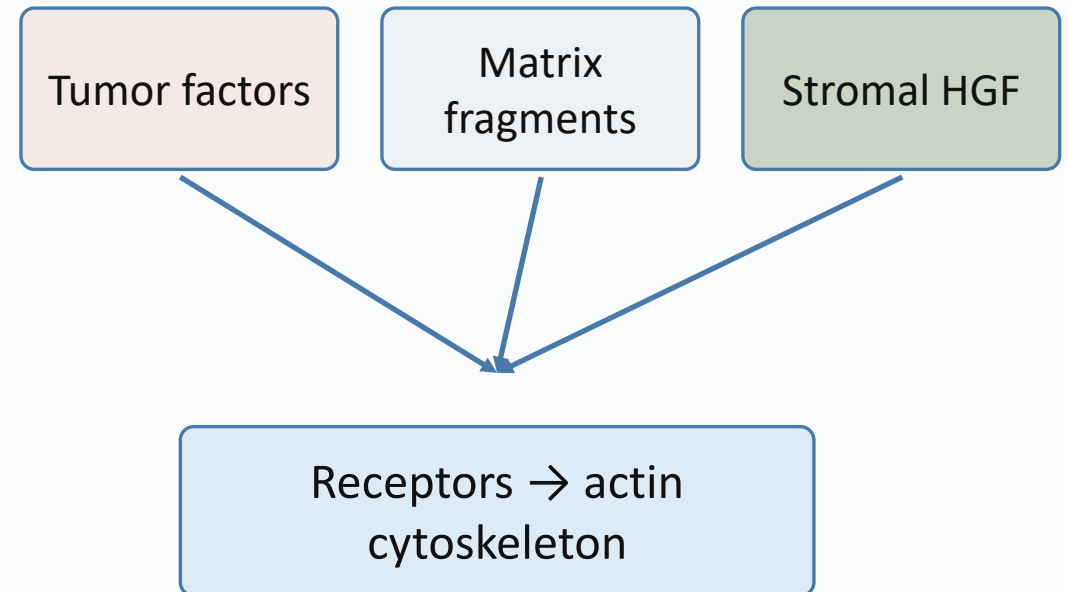
Matrix- and stroma-derived

- Collagen / laminin cleavage products
- Stromal HGF / scatter factor
- Paracrine and matrix-associated stimulation

The relevant motility cues vary across tumors

- Robbins does not assign one universal chemokine or growth-factor pathway to every tumor.
- Multiple receptors and signaling systems can converge on the cytoskeleton.
- Different cancers may achieve migration using different combinations of cues.

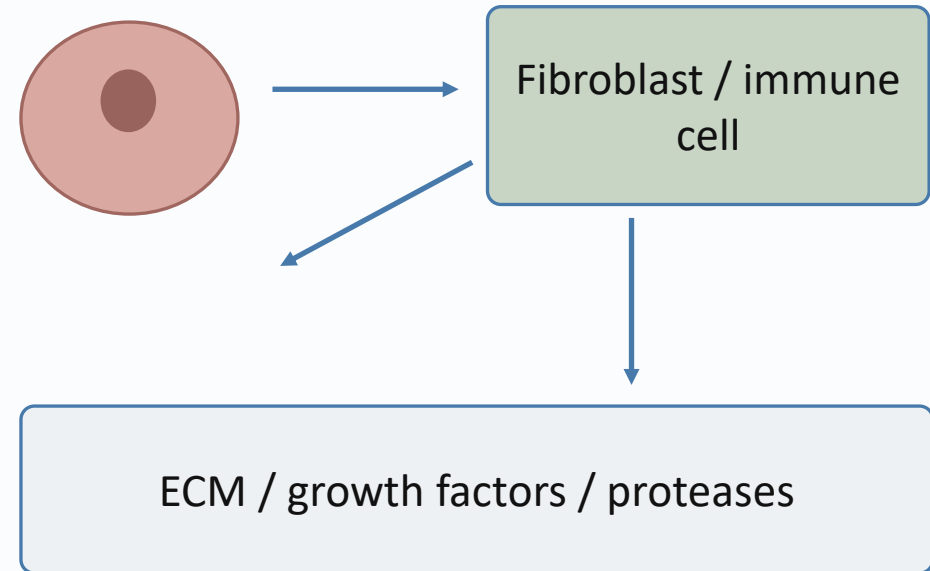
Schematic



Invasion is a tumor–stroma collaboration

- Tumor cells interact with fibroblasts, inflammatory cells, immune cells, and endothelium.
- Host-cell participation supplies proteases, ECM alterations, and motility cues.
- Invasion is therefore not a solely tumor-cell-autonomous process.

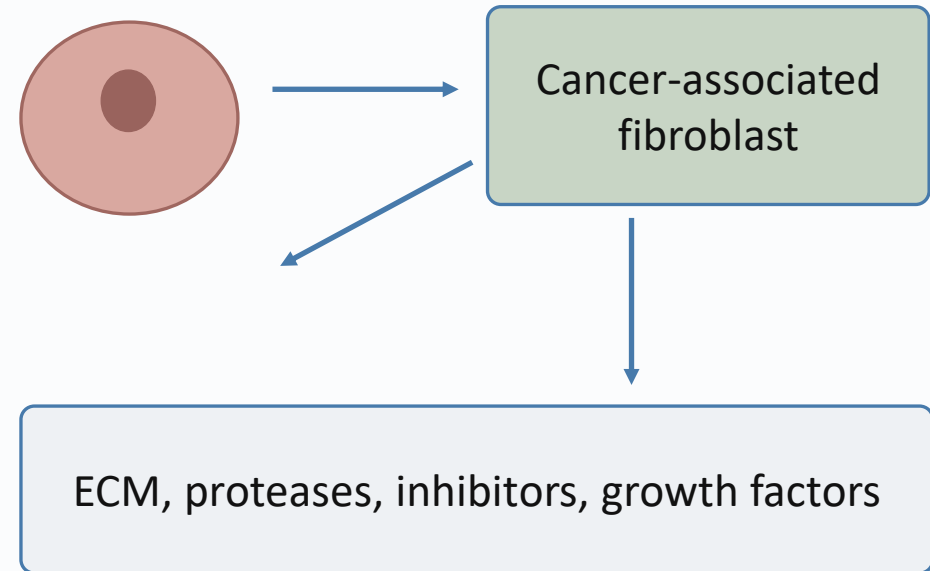
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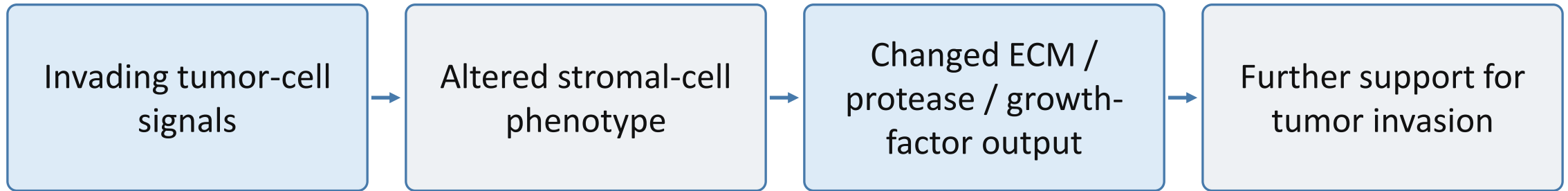
Cancer-associated fibroblasts remodel the niche

- Invading cancer cells can change fibroblast gene-expression programs.
- Cancer-associated fibroblasts alter ECM molecules, proteases, inhibitors, and growth factors.
- These changes may build a local environment that supports malignant behavior.

Schematic



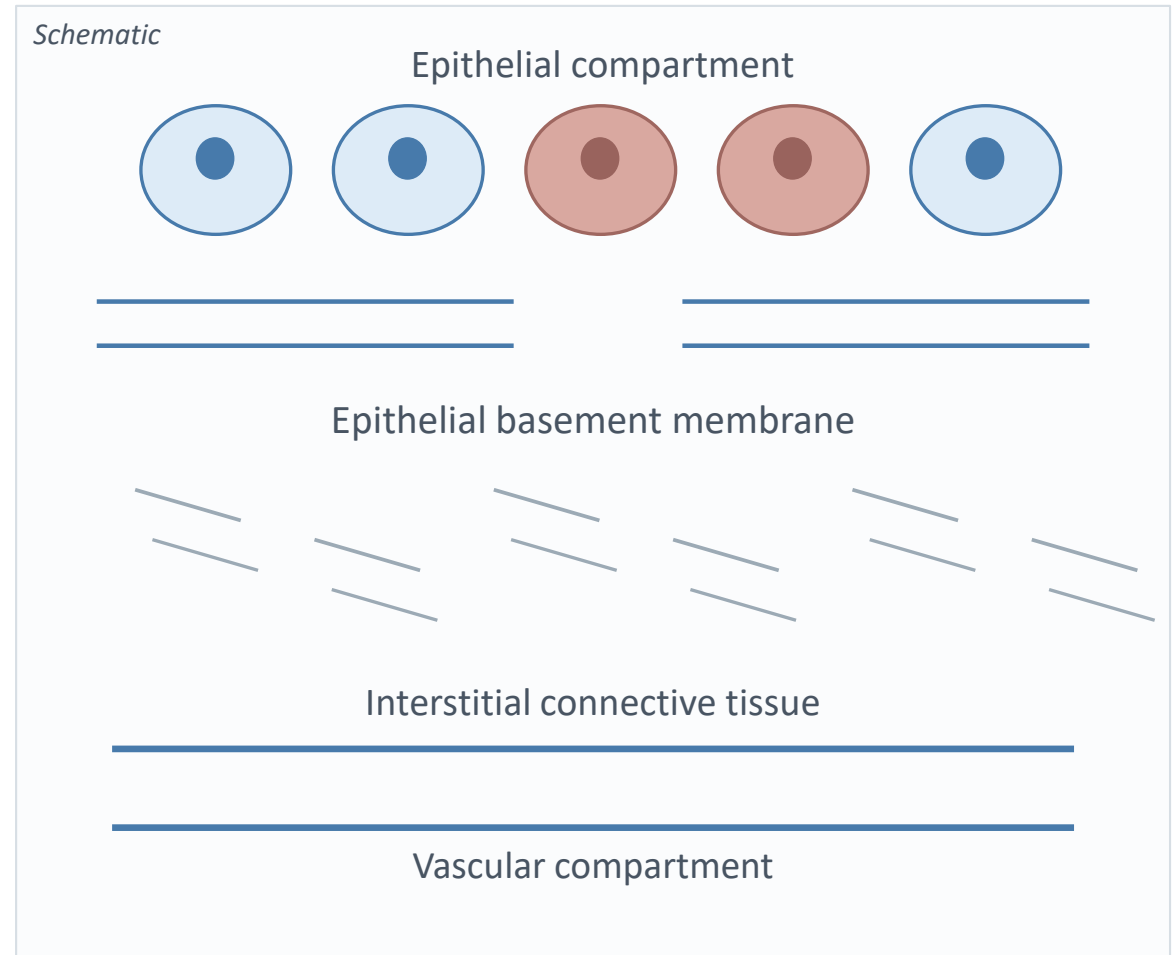
Tumor and stroma influence one another



A reciprocal interaction, not a fixed one-way process.

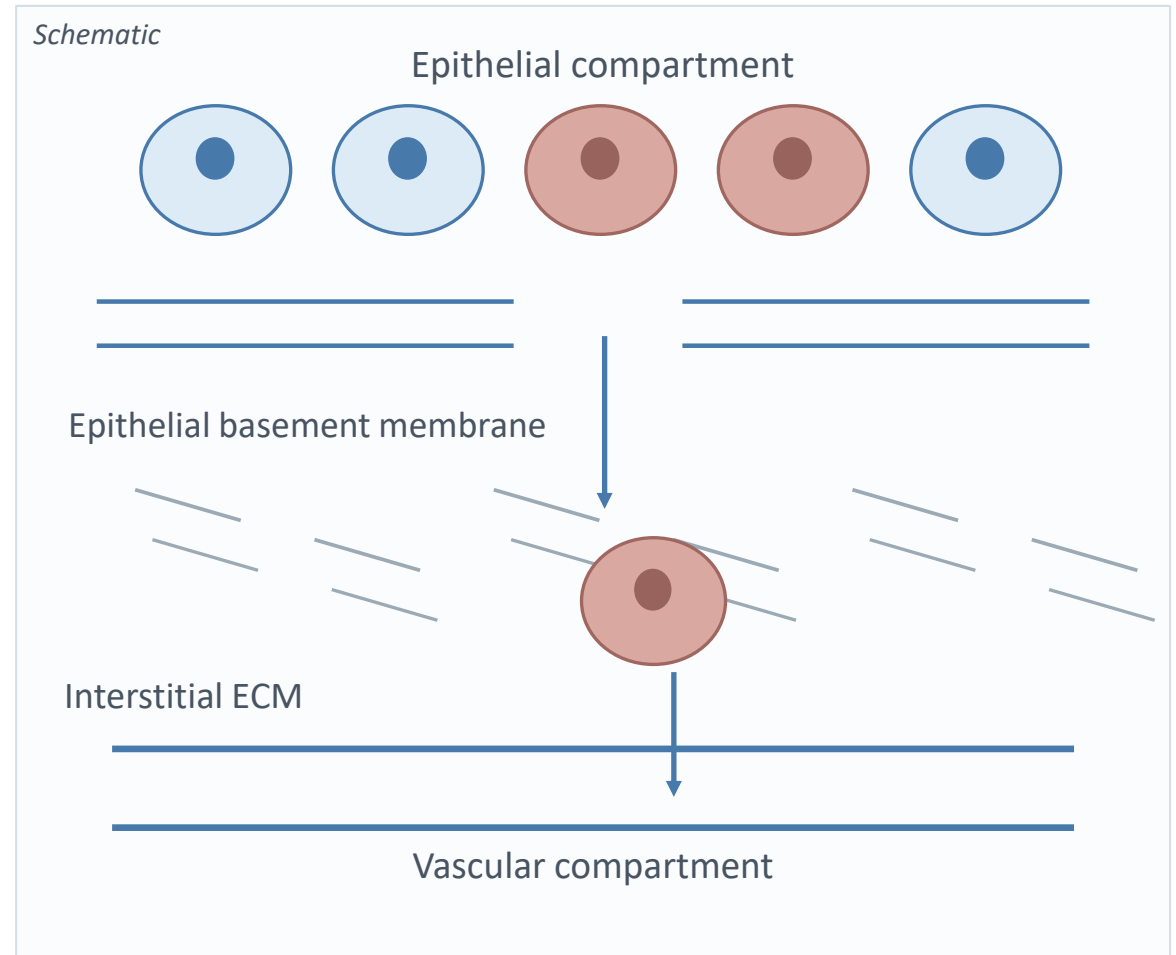
Immune and endothelial cells are part of the niche

- Innate and adaptive immune cells among interacting stromal populations.
- Endothelial cells form the next barrier to vascular entry.
- The exact cell-specific mechanisms remain incompletely defined account.



Intravasation is the local-phase endpoint

- Invading carcinoma cells penetrate the endothelial basement membrane.
- They then transmigrate into the vascular space.
- After vascular entry, survival and distant colonization are separate steps of the metastatic cascade.



Different barriers must be distinguished

Epithelial barrier

- Basement membrane below the primary epithelium
- Crossed during initial local invasion

Vascular barrier

- Endothelium and its basement membrane
- Crossed to reach the circulation

The first breach does not automatically mean intravasation.

A schematic boundary tests the concept of invasion

In two conceptual epithelial lesions, one has an intact basement membrane and the other has tumor cells beyond it. Which depicts stromal invasion?

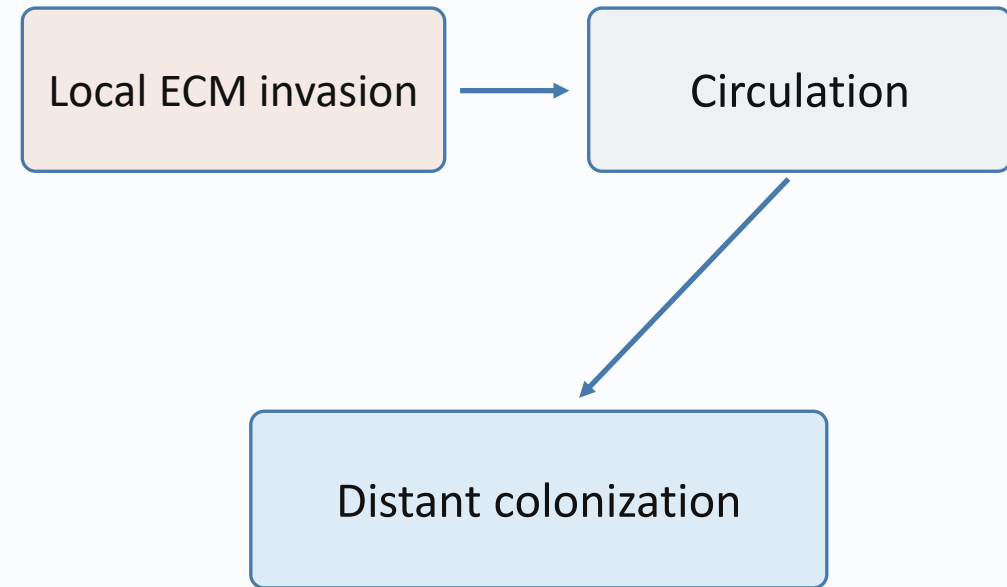
Mechanistic interpretation

- Tumor cells beyond a breached epithelial basement membrane represent stromal invasion in this schematic.
- This is a topological teaching example, not a patient specimen or full diagnostic rubric.
- The same matrix interactions explain how cells then move toward vessels.

Why high invasion does not imply high metastasis

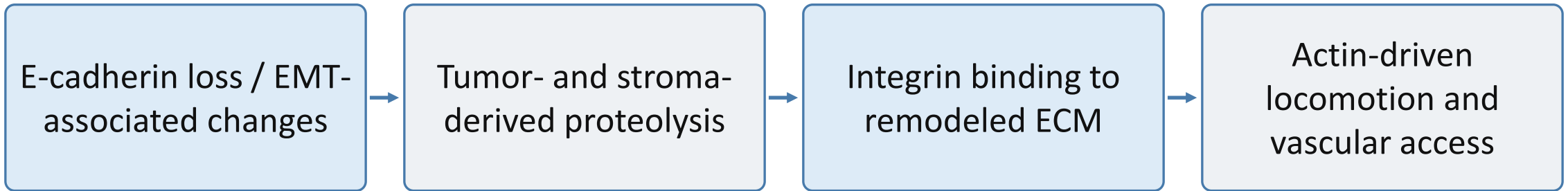
- Local tissue invasion is necessary but not sufficient for hematogenous metastasis.
- Cells still face survival, transport, arrest, extravasation, and colonization challenges.
- The overall inefficiency and complexity of successful metastasis.

Schematic



Separate later steps

Integrated mechanism: From cohesion loss to migration



Sequential model of invasion (schematic)

Predicting the effect of restoring cell adhesion

Which step of invasion would be most directly opposed if functional epithelial E-cadherin contacts were restored?

Mechanistic interpretation

- The dissociation/loosening stage would be most directly opposed.
- Effects on degradation or migration should not be assumed from E-cadherin restoration alone.
- The invasion phenotype integrates multiple pathways.

Predicting the effect of lower protease activity

What immediate ECM-level consequence is expected when functional matrix degradation is reduced?

Mechanistic interpretation

- Basement membrane and interstitial matrix are less readily remodeled.
- Generation of matrix cleavage fragments and liberation of stored factors may also decrease.
- Compensation by other proteases or stromal pathways is possible.

Predicting the effect of failed rear-edge release

A tumor cell makes new leading-edge attachments but cannot release its trailing edge. Why may net movement be impaired?

Mechanistic interpretation

- Movement requires coordinated formation and disassembly of adhesions.
- A persistently attached rear can oppose cell-body translocation.
- Motility reflects the entire actin–adhesion cycle.

Predicting the effect of impaired MET signaling

If HGF–MET motility signaling is reduced, which input is directly affected?

Mechanistic interpretation

- The stromal HGF/scatter-factor paracrine motility input is affected.
- Other autocrine or matrix-derived cues may still operate.
- Robbins does not imply that MET is the only route to invasion.

Four mechanisms, four representative molecules

Adhesion / proteolysis

- E-cadherin: Epithelial cell–cell cohesion
- MMP9: Collagen IV cleavage and growth-factor release

ECM interaction / movement

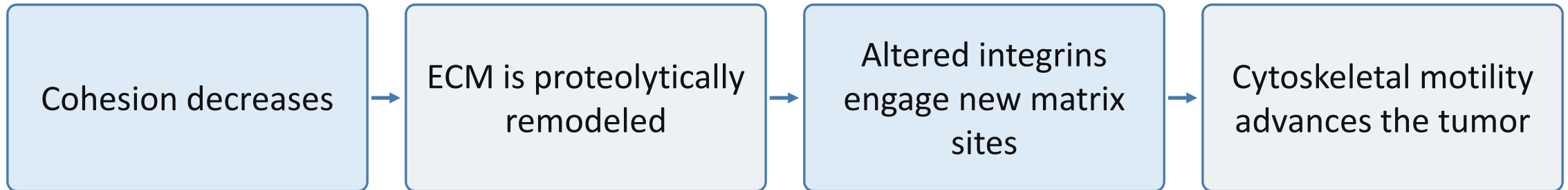
- Integrins: Attachment and survival signaling
- MET: Receptor for stromal HGF motility cue

Representative examples are not exclusive biomarkers of invasive cancer.

Common interpretive errors

- Do not equate reduced E-cadherin with proof of completed metastasis.
- Do not treat MMP9 expression as a universal quantitative diagnostic cutoff.
- Do not portray proteolysis as merely mechanical, or EMT as mandatory in every tumor.
- Do not omit fibroblasts and immune cells from an invasion mechanism.

Four-step mechanism at a glance



A coordinated, microenvironment-dependent process leading toward vascular access.

References and interpretation boundary

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026), Chapter 7, “Invasion of Extracellular Matrix,” printed pp. 274–275.
- Context: Chapter 7, “Invasion and Metastasis”; Chapter 1, ECM/integrin background.
- Original editable schematics in this lecture are conceptual representations, not source-figure reproductions or histologic specimens.