

# **Vascular Dissemination, Homing, and Colonization**

The distant phase of the metastatic cascade

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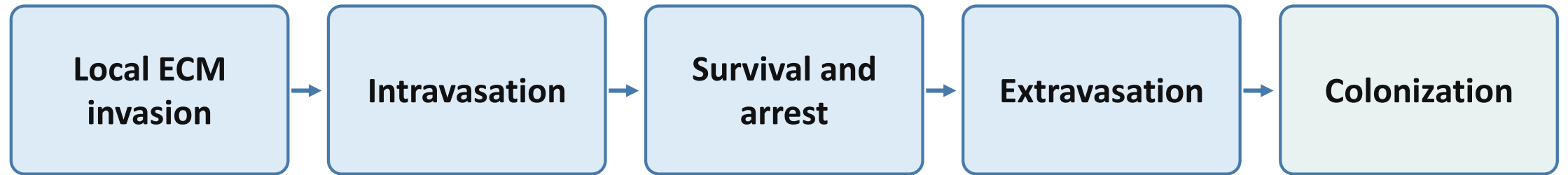
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# Learning objectives

- Distinguish vascular dissemination, tissue homing, extravasation, and colonization.
- Explain why circulating tumor cells rarely produce overt metastases.
- Interpret vascular drainage, organ tropism, and tumor dormancy.
- Trace a tumor–stromal feedback loop in bone metastasis.

*Mechanistic lecture with clinicopathologic examples.*

## The metastatic cascade has two linked phases



- This lecture emphasizes the vascular and distant-organ phases.

# Invasion and metastasis are distinct properties

## Local invasion

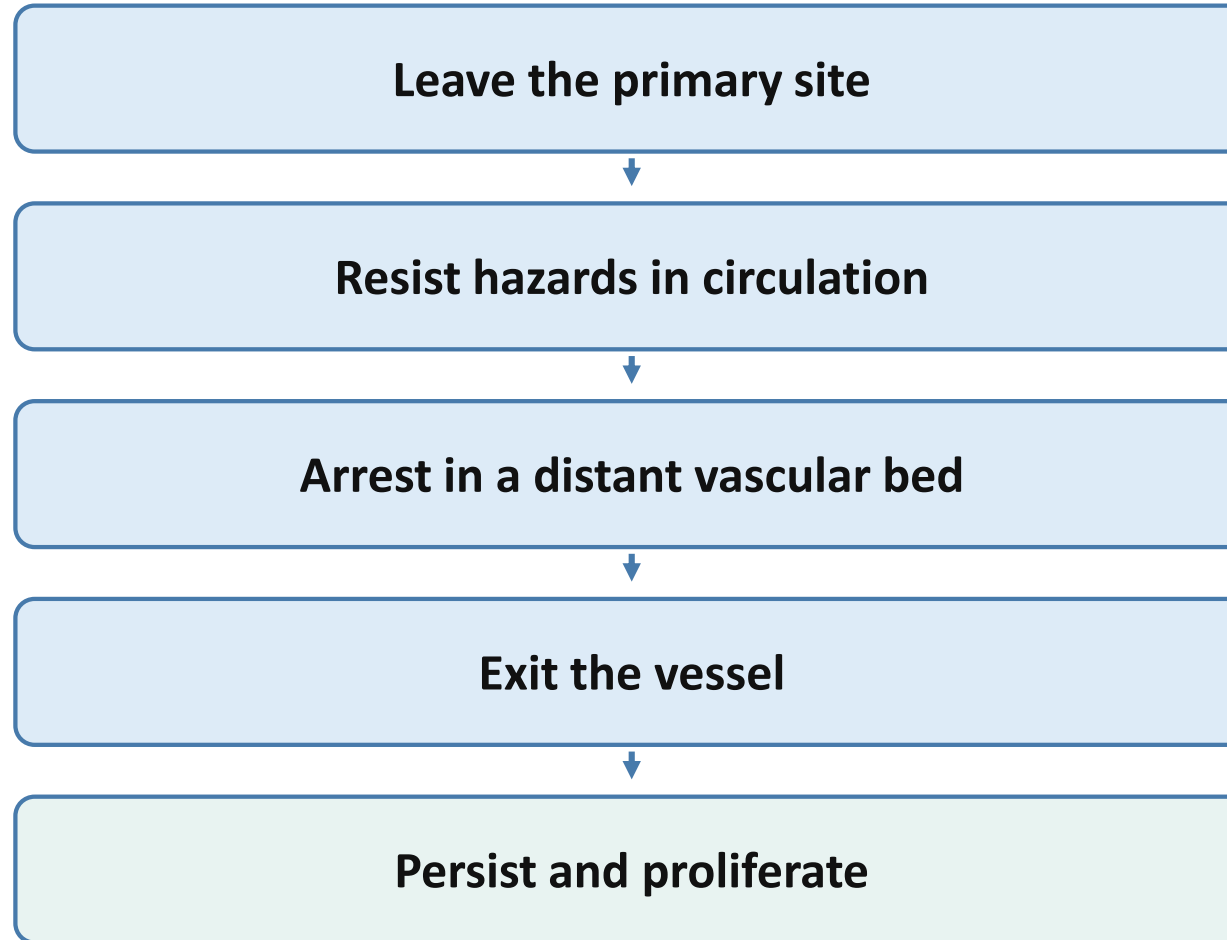
- Tumor breaches basement membrane and interstitium.
- Vascular access becomes possible.

## Metastatic spread

- Tumor establishes growth at a discontinuous site.
- Requires survival and adaptation after dispersal.

*Invasion is a prerequisite for many solid-tumor metastases, not a guarantee.*

# A journey with sequential bottlenecks



*A failure at any stage can prevent a clinically apparent metastasis.*

## Why hematogenous metastasis is inefficient

- Large numbers of locally invasive tumor cells may enter the bloodstream.
- Only a small minority give rise to established metastatic tumors.
- Success depends on multiple tumor-cell and host-cell interactions.

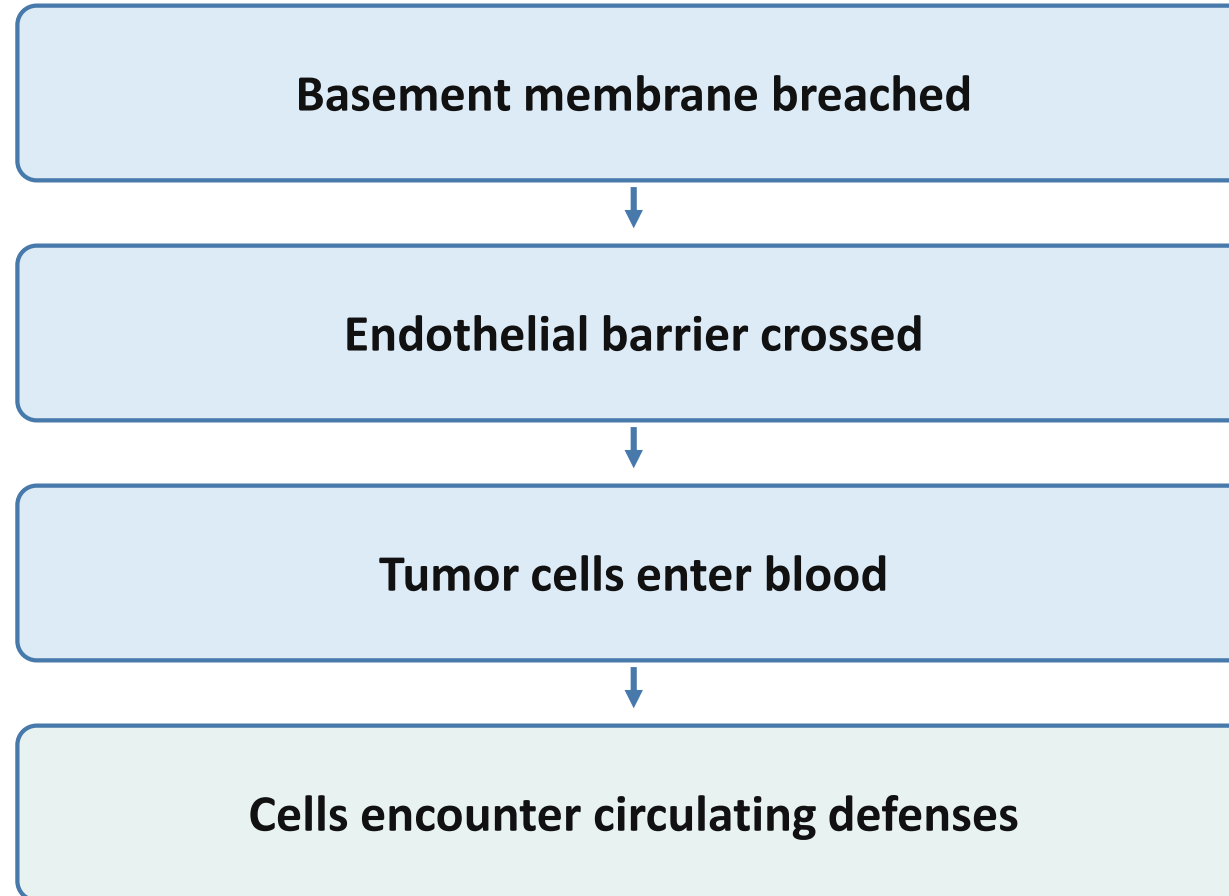
*Many circulating tumor cells ≠ many metastatic lesions.*

## Metastatic competence is multifactorial

- No single universal “metastasis gene” explains the cascade.
- Complementary genetic and epigenetic changes may be needed.
- Distinct subclones may provide different required capabilities.

*Cooperation within heterogeneous tumor-cell groups is a plausible mechanism.*

## The vascular phase begins after intravasation



*Intravasation follows local ECM degradation and migration.*

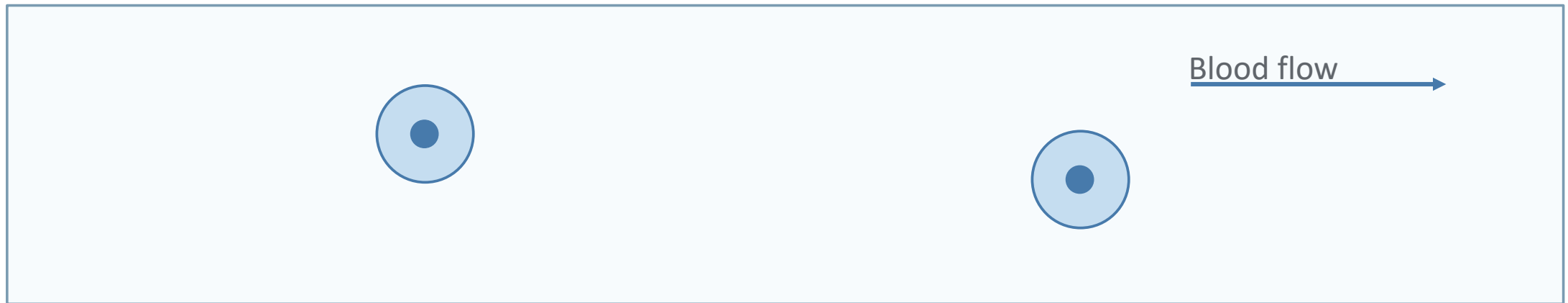
## Blood exposes tumor cells to three major threats

- Mechanical shear stress during circulation.
- Anoikis, apoptosis induced by loss of appropriate anchorage.
- Innate and adaptive immune defense mechanisms.

*Survival in blood is an active biological challenge.*

# Shear stress threatens circulating tumor cells

Schematic: Circulating malignant cells and blood elements



- Fluid flow creates mechanical forces on freely circulating cells.
- The vascular environment differs from a protected tissue niche.

## Anoikis is the price of losing anchorage

### Normal epithelial cell

- Loses attachment to extracellular matrix.
- May activate apoptosis (anoikis).

### Metastatic tumor cell

- Must resist attachment-loss signals.
- May use altered integrin-associated survival signaling.

*Anoikis resistance assists survival after detachment.*

## Immune defenses remain a systemic barrier

- Innate responses and adaptive responses can destroy circulating cancer cells.
- Metastasizing cells must evade surveillance while traveling through blood.
- Immune evasion is one challenge among several, not the complete explanation.

*The source identifies defense categories; Specific checkpoints are outside this unit.*

# Viability is not the same as metastatic competence

## **Viable circulating cell**

- Has survived hazards of the bloodstream.
- May still lack traits needed for distant growth.

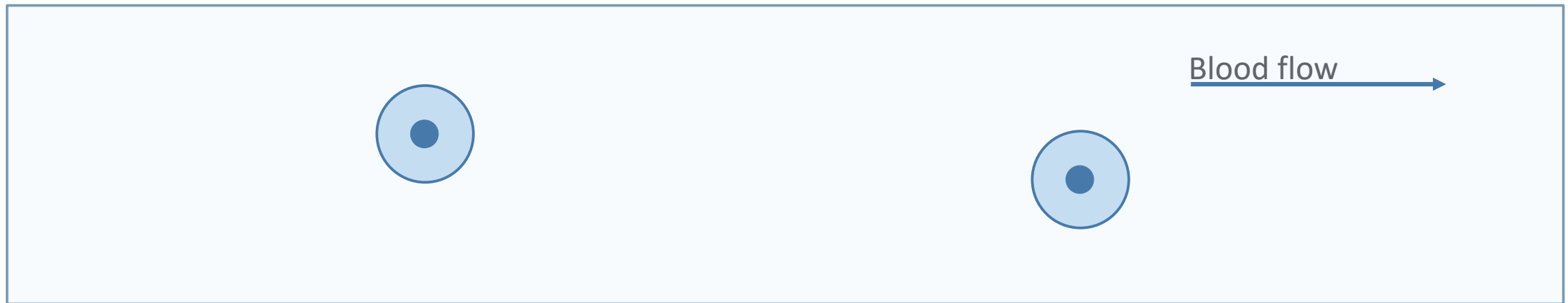
## **Metastasis-forming cell**

- Must arrest, extravasate, and persist.
- Must adapt to a novel tissue environment.

*Circulating tumor cells are detectable, but not all are founders of metastases.*

## A circulating tumor cell may travel alone

Schematic: Circulating malignant cells and blood elements

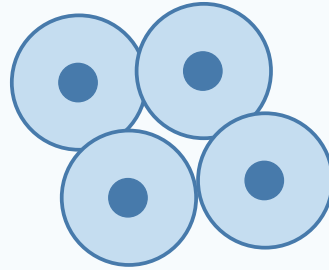


- Individual cells can be exposed to blood-borne stresses.
- Single-cell dissemination does not establish that colonization will occur.

# Multicellular aggregates offer a potential advantage

Schematic: Circulating malignant cells and blood elements

**Homotypic cell cluster**



- Tumor cells can travel as cohesive multicellular groups.
- Evidence favoring aggregates among metastatic founders.

## Two types of cell–cell interaction form emboli

### Homotypic

- Tumor cell  $\leftrightarrow$  tumor cell.
- Creates cohesive cancer-cell aggregates.

### Heterotypic

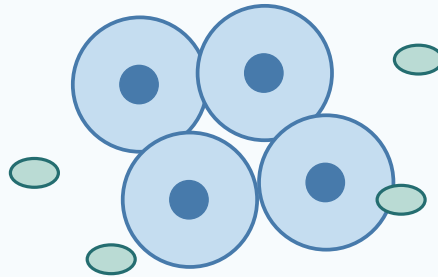
- Tumor cell  $\leftrightarrow$  circulating blood element.
- Platelets are especially emphasized.

*Both interactions can support circulating tumor-cell clumping.*

# Platelets interact with tumor-cell aggregates

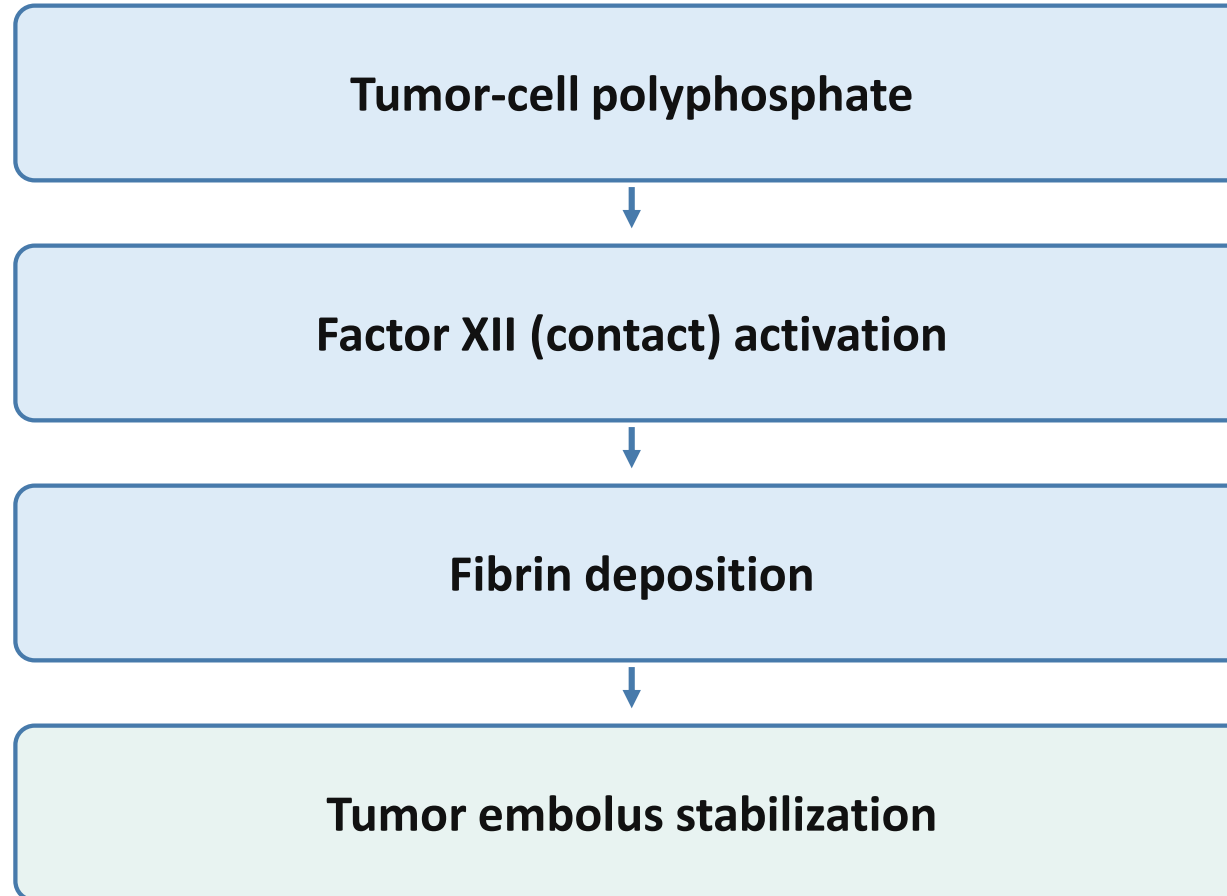
Schematic: Circulating malignant cells and blood elements

**Platelet-associated  
aggregate**



- Platelets associate with tumor cells in the blood.
- These interactions are believed to enhance tumor-cell survival.

# A coagulation-linked route to tumor emboli



*This as a possible mechanism, not a universal feature.*

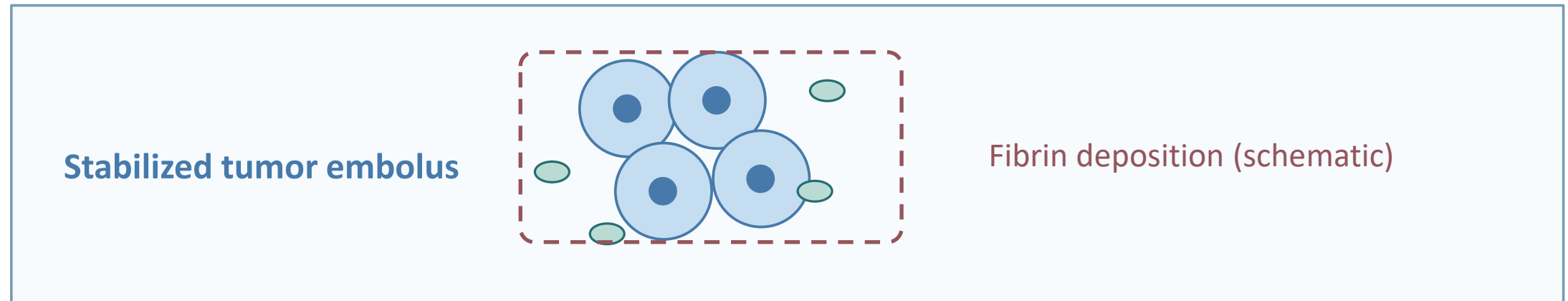
## Polyphosphate is one proposed initiator

- Some tumors express anionic substances such as polyphosphate.
- Polyphosphate may activate factor XII in the contact pathway.
- This can lead to local fibrin deposition around aggregates.

*Use conditional language: “some,” “may,” and “potentially.”*

# Fibrin can consolidate tumor emboli

Schematic: Circulating malignant cells and blood elements



- Fibrin deposition may stabilize a multicellular embolus.
- Stabilized emboli may arrest together in capillary beds.

## Why arresting as a group might matter

### Circulating single cell

- Must independently withstand bloodstream stress.
- Must individually possess founder capabilities.

### Circulating cell group

- Can aggregate with platelets and fibrin.
- May collectively supply complementary traits.

*These are mechanistic proposals, not guarantees of clinical metastasis.*

## Clusters may contain complementary subclones

- Different tumor cells may contribute different metastasis-related traits.
- Collaborative migration can therefore be biologically advantageous.
- Collective behavior is compatible with tumor heterogeneity.

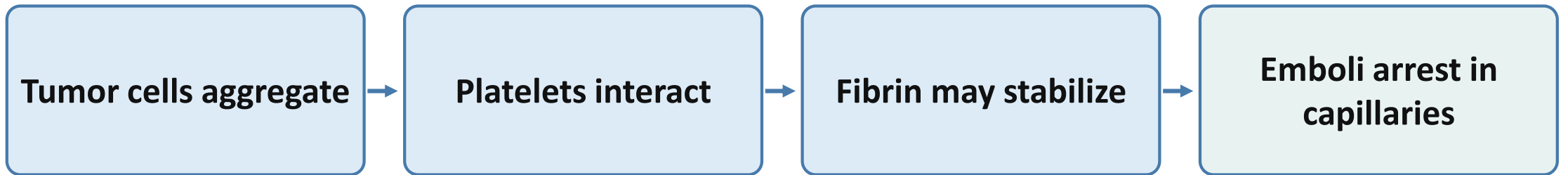
*The specific contribution of each subclone cannot be presumed.*

## Stem cell–like traits matter to metastatic founders

- Self-renewing cells may sustain prolonged growth at a distant site.
- Plasticity may help adaptation to a foreign microenvironment.
- A cell group may be more likely to contain needed stem cell–like capabilities.

*Stemness is a proposed component of successful colonization.*

## From aggregate formation to vascular arrest



- Arrest is an intermediate stage; Extravasation and outgrowth must follow.

# Three determinants of metastatic distribution

**Vascular drainage from the primary**



**Organ-specific tumor tropism**



**Escape from tumor dormancy**

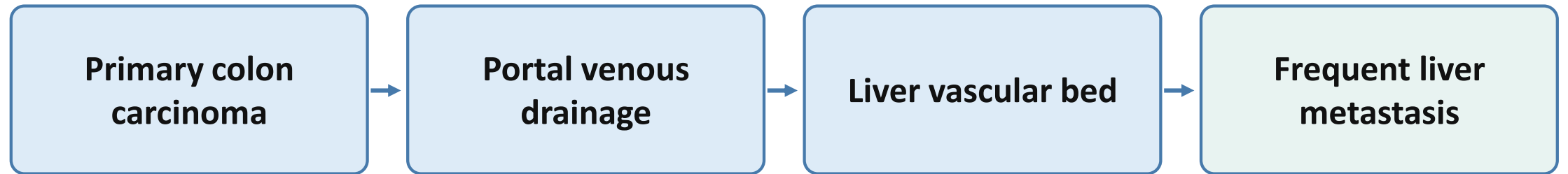
*These govern where circulating cells stop and which deposits become clinically significant.*

## Vascular drainage provides a first-pass filter

- Tumor cells enter vessels connected to the primary tumor.
- The first downstream capillary bed can trap disseminated cells.
- Lung and liver are common sites in the first-pass framework.

*Anatomical blood flow predicts some—but not all—patterns.*

## Colon carcinoma illustrates portal drainage



- The liver is the first major organ downstream for many colorectal primaries.

## The “first capillary bed” principle

| Anatomical factor | Expected implication                 | Important qualification       |
|-------------------|--------------------------------------|-------------------------------|
| Venous drainage   | Directs circulating cells downstream | Does not explain all tropisms |
| Capillary arrest  | Can retain tumor emboli              | Arrest is not outgrowth       |
| Liver and lung    | Common first-pass destinations       | Other organs may be preferred |

*Both anatomy and tumor biology influence distribution.*

## Anatomy alone cannot account for tropism

- Several cancers preferentially metastasize to particular organs.
- Those preferences cannot be reduced to first-pass vascular trapping.
- Adhesion, chemotaxis, and tissue permissiveness provide additional explanations.

*Do not confuse circulation pathways with organ-specific biological selection.*

## Classic organ-tropism examples

| Primary neoplasm   | Favored metastatic sites |
|--------------------|--------------------------|
| Prostate carcinoma | Bone                     |
| Breast carcinoma   | Bone                     |
| Lung carcinoma     | Adrenal glands; brain    |
| Neuroblastoma      | Liver; bone              |
| Ocular melanoma    | Liver                    |

*Examples are tendencies, not exclusive metastatic destinations.*

## Breast and prostate carcinomas favor bone

- Bone is a characteristic target for these tumors.
- This is a departure from a drainage-only prediction.
- Later slides explain a breast cancer–bone microenvironment feedback mechanism.

*A favored site does not imply that every tumor follows this route.*

## Lung carcinoma may involve adrenals and brain

- The source highlights adrenal and brain metastases from lung carcinoma.
- Organ-specific preferences suggest mechanisms beyond simple trapping.
- Brain endothelium is additionally relevant to extravasation biology.

*Site patterns motivate mechanistic questions; They are not diagnostic rules.*

## Neuroblastoma and ocular melanoma show tropism

- Neuroblastoma is described as spreading to liver and bone.
- Ocular melanoma has a striking tendency to metastasize to liver.
- Both illustrate selective destination patterns across tumor types.

*“Seed” characteristics and “soil” characteristics must be considered together.*

# Three complementary biological explanations

**Endothelial adhesion molecule matching**



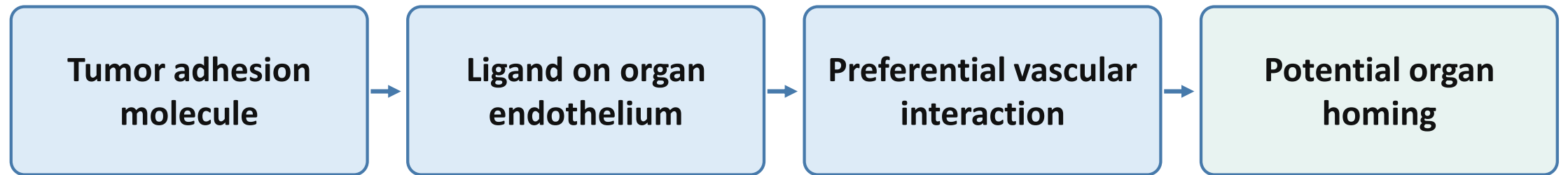
**Chemokine-guided cell trafficking**



**Supportive destination microenvironment**

*Any one mechanism is not established as a universal determinant.*

## Adhesion receptors can mediate tissue targeting



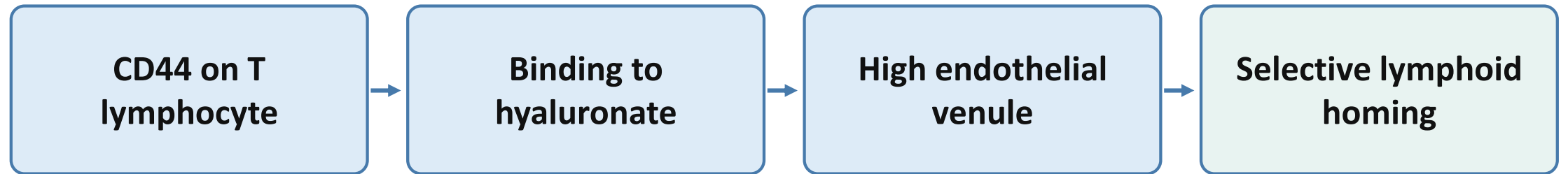
- Specific receptor–ligand matching may favor colonization of particular organs.

## CD44 links normal trafficking to cancer homing

- CD44 is expressed on normal T lymphocytes.
- It participates in selective lymphocyte migration to lymphoid tissues.
- Solid cancers often express CD44, potentially enhancing dissemination.

*This example illustrates reuse of normal cell-trafficking machinery.*

## CD44 and hyaluronate: The physiological model



- The physiologic receptor–ligand example motivates tumor homing models.

# CD44 in normal and malignant settings

## Normal immune trafficking

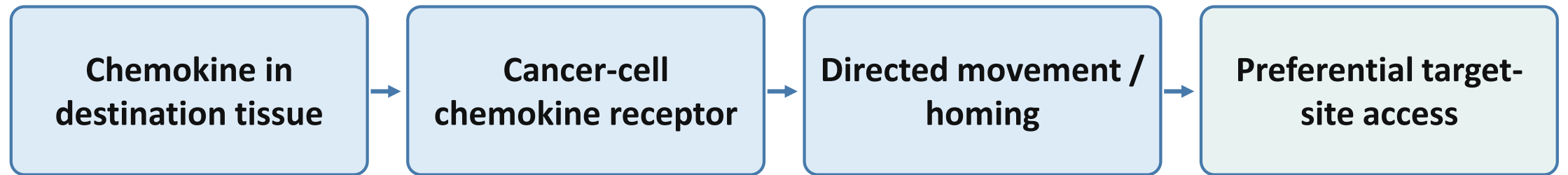
- CD44-bearing T lymphocytes.
- Hyaluronate on high endothelial venules.

## Solid-tumor dissemination

- CD44 often expressed by tumor cells.
- Expression appears to facilitate lymph node and other spread.

*Association with spread does not alone prove an organ-specific causal mechanism.*

## Chemokine gradients may help direct cancer cells



- This parallels chemokine-directed trafficking of immune cells.

# Adhesion versus chemokine guidance

## Adhesion-based homing

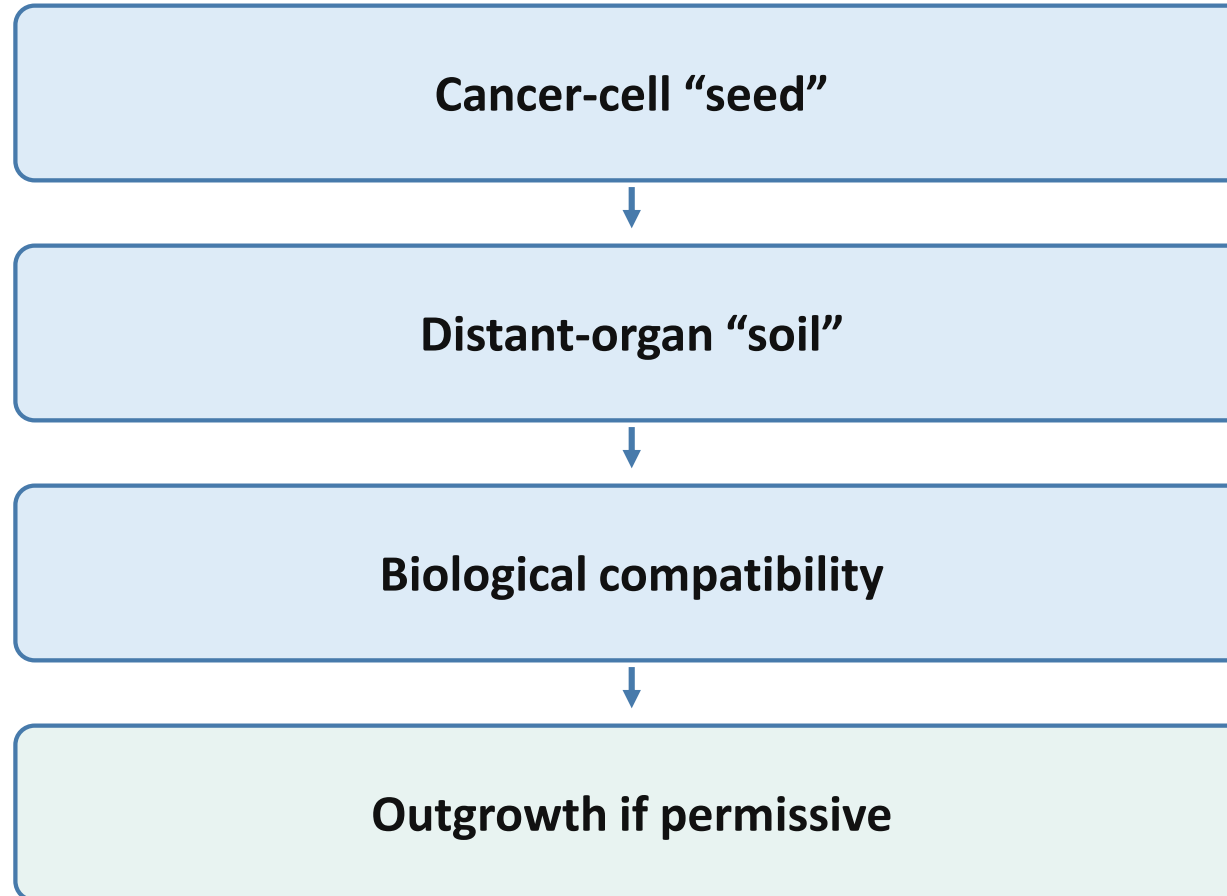
- Receptor engages an endothelial ligand.
- Promotes selective vascular attachment.

## Chemokine-based homing

- Receptor detects a tissue chemoattractant.
- Can influence tumor-cell movement.

*Both are plausible contributors to organ tropism.*

# The seed–soil model concerns compatibility



*Stephen Paget's hypothesis emphasizes colonization, not simply blood flow.*

## A well-perfused site may still resist metastasis

### Permissive soil

- Supports cancer-cell persistence.
- Can provide tumor-supporting signals.

### Nonpermissive soil

- Unfavorable for distant tumor growth.
- May remain metastasis-poor despite vascular supply.

*Skeletal muscle and spleen are textbook examples of relatively nonpermissive sites.*

## Skeletal muscle illustrates nonpermissive soil

- Skeletal muscle receives substantial blood flow.
- Yet metastatic deposits are comparatively unusual there.
- This mismatch challenges a purely hemodynamic explanation.

*A tissue can receive tumor cells but fail to support expansion.*

## The spleen illustrates the same paradox

- The spleen is richly vascularized.
- Nevertheless, metastases are relatively rare.
- Blood delivery does not imply successful seeding and colonization.

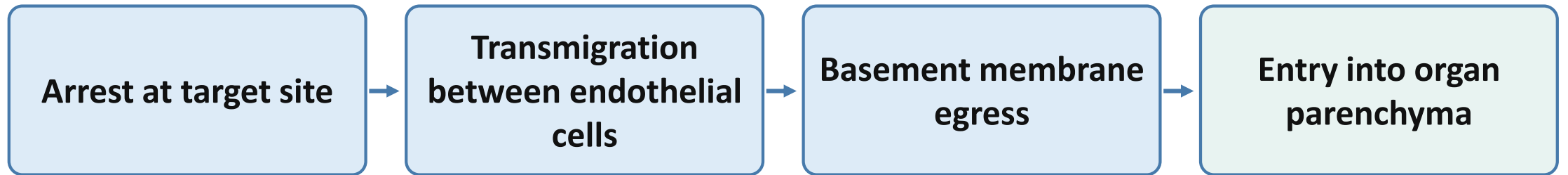
*The primary teaching point is tissue permissiveness, not absolute immunity.*

## Separate arrival from establishment

| Process                | Question                          | What it establishes            |
|------------------------|-----------------------------------|--------------------------------|
| Vascular delivery      | Do cells reach the organ?         | Opportunity for arrest         |
| Adhesion / chemotaxis  | Do cells preferentially interact? | Potential tissue tropism       |
| Local microenvironment | Can cells survive and grow?       | Productive colonization        |
| Dormancy escape        | Do surviving cells expand?        | Clinically apparent metastasis |

*These stages are related but not interchangeable.*

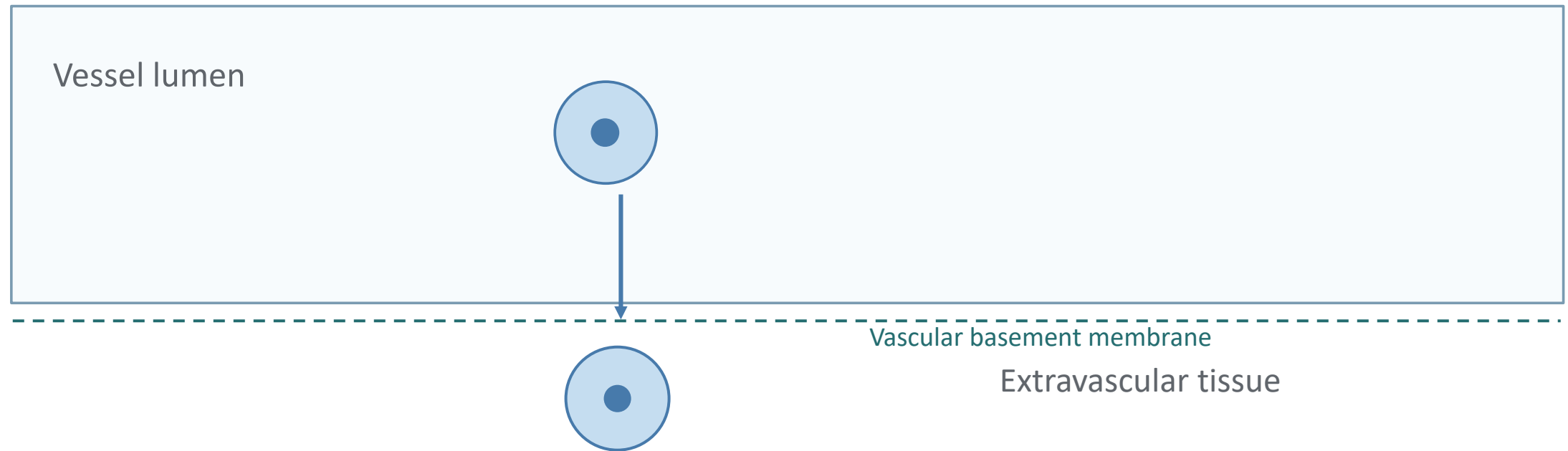
## Extravasation begins after vascular arrest



- Extravasation is tissue entry; It does not itself establish a growing lesion.

# Tumor cells must cross an endothelial barrier

Schematic tissue entry after capillary arrest



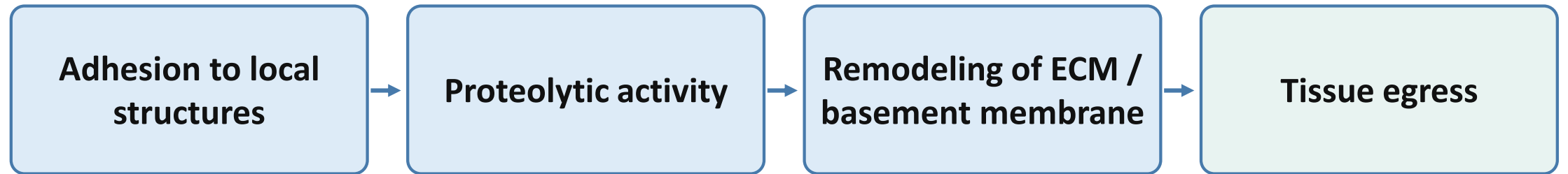
- Cells exit through or between elements of the vessel lining.
- They then traverse the endothelial basement membrane.

## Adhesion molecules assist extravasation

- Integrins participate in adhesion during distant tissue entry.
- Laminin receptors can contribute to basement-membrane interactions.
- Successful passage depends on coordinated cell–matrix interactions.

*This mirrors, but is not identical to, local tumor-cell invasion.*

## Proteases enable movement through barriers



- The source identifies proteases as required effectors without a universal enzyme list.

## Chemokines also influence extravasation

- Chemokines may originate from cancer cells.
- They may also be supplied by host innate immune cells.
- Their effects can assist movement into the extravascular compartment.

*Source emphasizes multiple interacting cell populations.*

# Tumor cells are not the only cellular actors

## Cancer cells

- Provide adhesion receptors and proteases.
- May produce chemokines.

## Innate immune cells

- Monocytes and neutrophils contribute signals.
- Can provide chemokines that facilitate extravasation.

*The tissue-entry process is a tumor–host interaction.*

# Endothelial architecture changes the challenge

## Fenestrated endothelium

- Representative sites: Liver and bone marrow.
- Structural context may affect cell passage.

## Tight junctions

- Representative site: Brain.
- A different barrier architecture is encountered.

*Exact extravasation mechanisms remain incompletely understood.*

## What remains uncertain about extravasation

- The detailed mechanisms are not fully resolved.
- Mechanisms may vary between fenestrated and tightly joined endothelium.
- A single universal model is therefore not justified.

*Avoid presenting a specific route across all organ endothelia as established.*

# Survival after arrival need not mean outgrowth

## Distant persistence

- Tumor cells can remain viable at distant sites.
- Growth may be absent or clinically occult.

## Productive colonization

- Tumor cells expand into a secondary mass.
- Requires adaptation and supportive host interactions.

*Dormancy separates arrival from overt metastasis.*

## Tumor dormancy: A clinically important state

- Disseminated tumor cells may survive yet fail to proliferate into a detectable lesion.
- This dormant state can persist at a distant site.
- Escape from dormancy is among the determinants of apparent metastatic deposits.

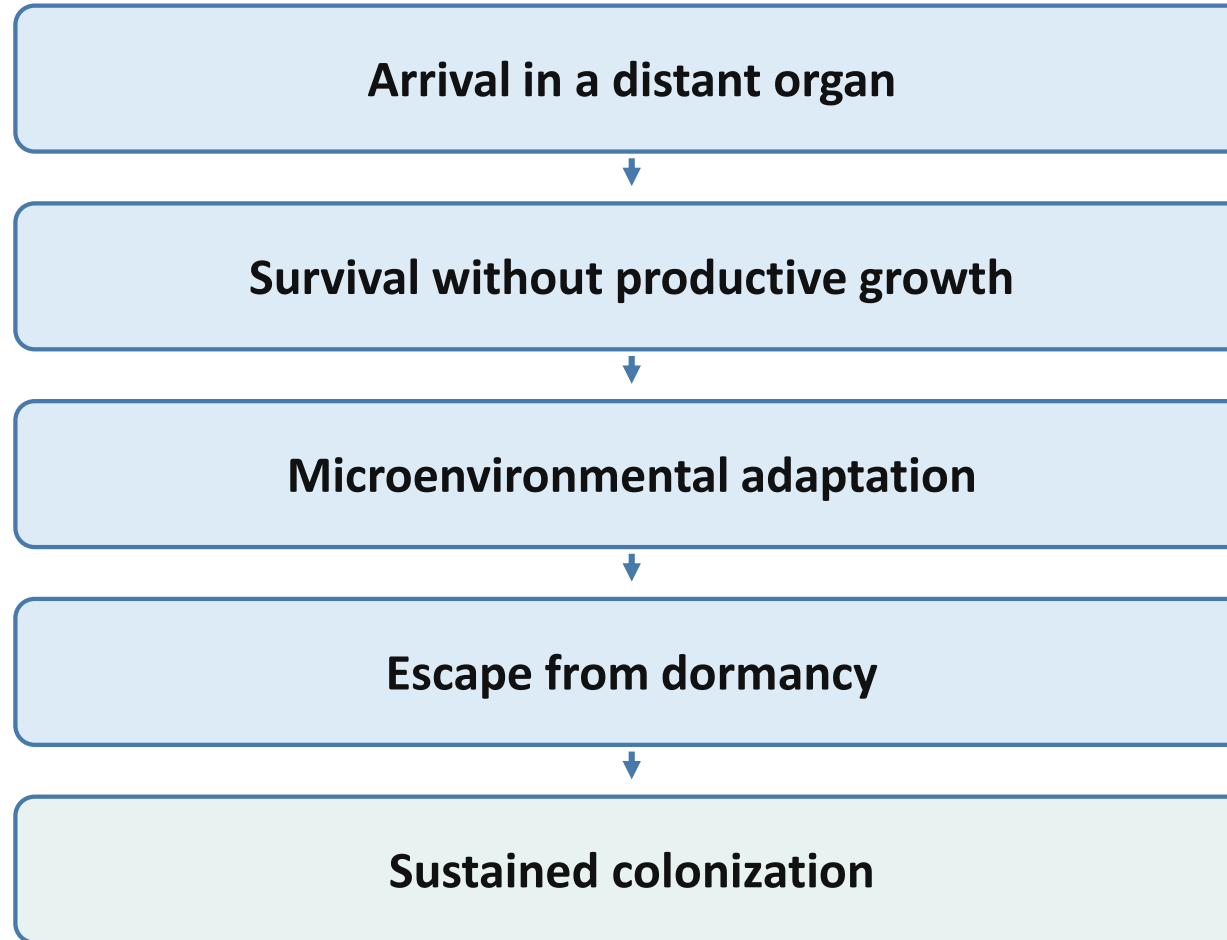
*Dormancy is not the same as elimination of disseminated cells.*

## Tumors in which dormancy is well described

| Tumor example      | Relevance to dormancy                                    |
|--------------------|----------------------------------------------------------|
| Melanoma           | Distant cells may persist without immediate outgrowth    |
| Breast carcinoma   | Delayed metastatic outgrowth is compatible with dormancy |
| Prostate carcinoma | Long-lived disseminated cells are a recognized concept   |

*These examples; No time interval or clinical rate is implied.*

# From dormancy to an overt metastatic lesion



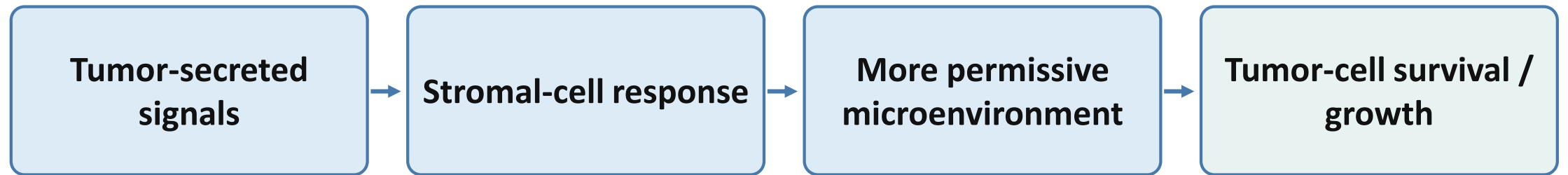
*Specific triggers of escape remain incompletely characterized.*

## Metastatic niches involve resident stromal cells

- Cancer cells can secrete cytokines, growth factors, and ECM molecules.
- These signals act on host stromal cells at the metastatic site.
- Altered stromal responses can make the local environment more hospitable.

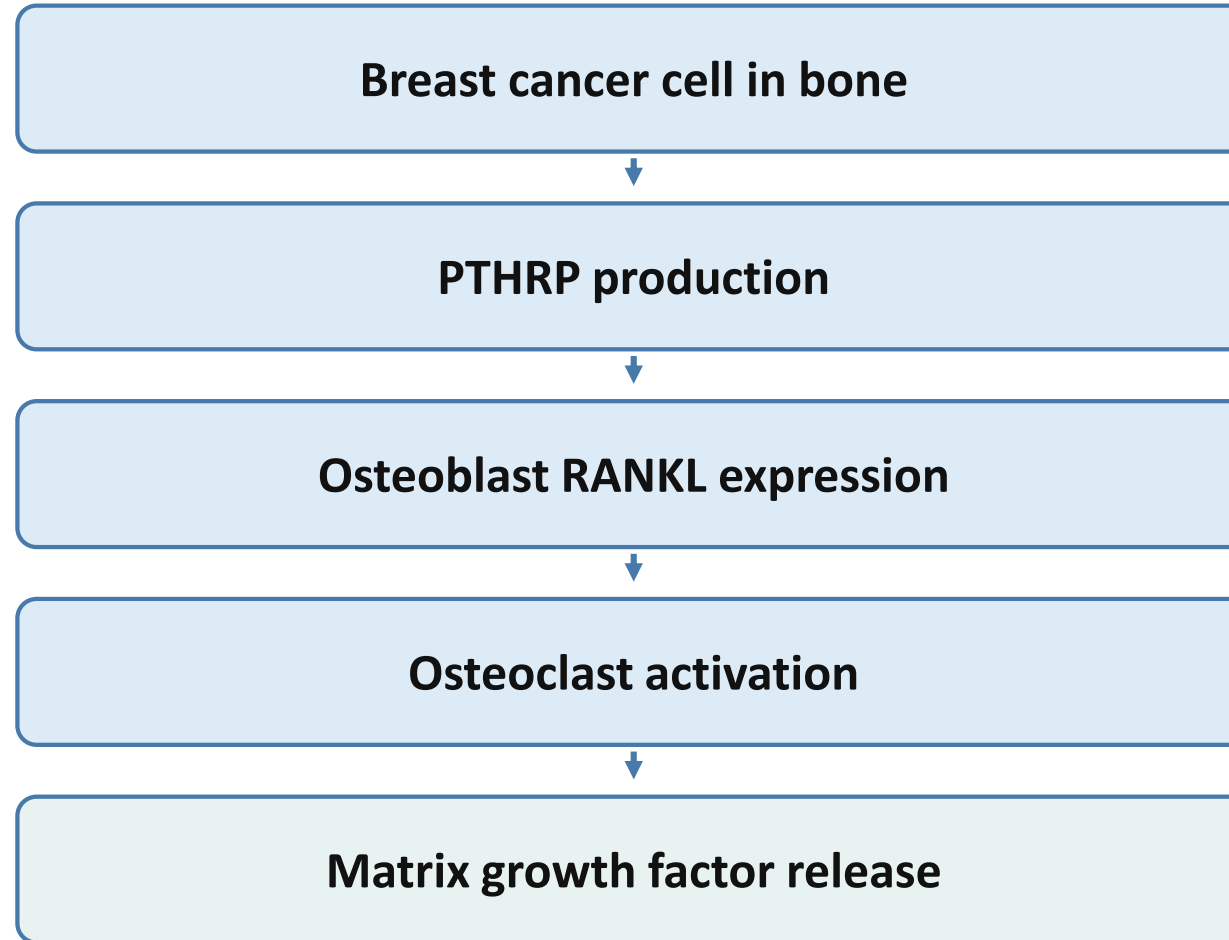
*A metastatic deposit is an ecosystem, not only a population of cancer cells.*

## Tumor–stroma communication is reciprocal



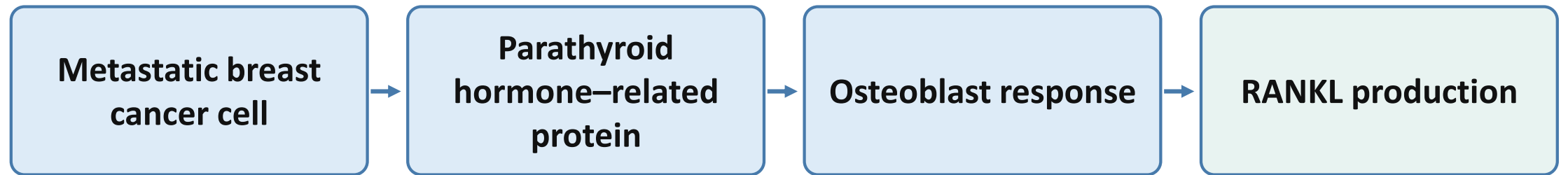
- Many additional feedback loops likely exist but are not fully delineated.

# Bone metastasis provides a defined feedback model



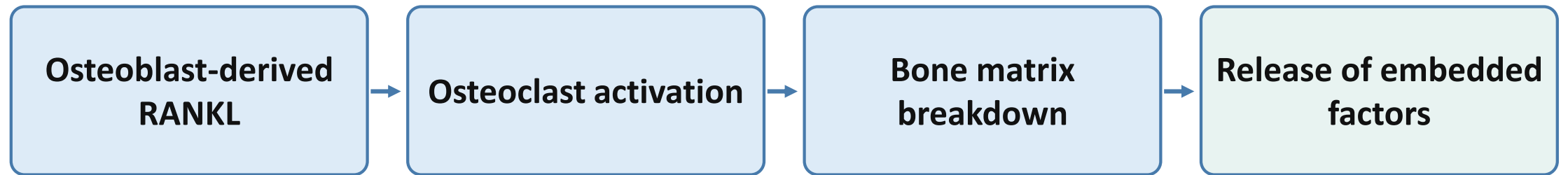
*IGF and TGF- $\beta$  then support signaling in cancer cells.*

## Tumor-derived PTHRP acts on osteoblasts



- PTHRP is upstream of RANKL in the cited example.

## RANKL activates osteoclasts



- This pathway recruits bone-resorbing cells to support the metastatic niche.

## Osteoblasts and osteoclasts play different roles

### Osteoblast

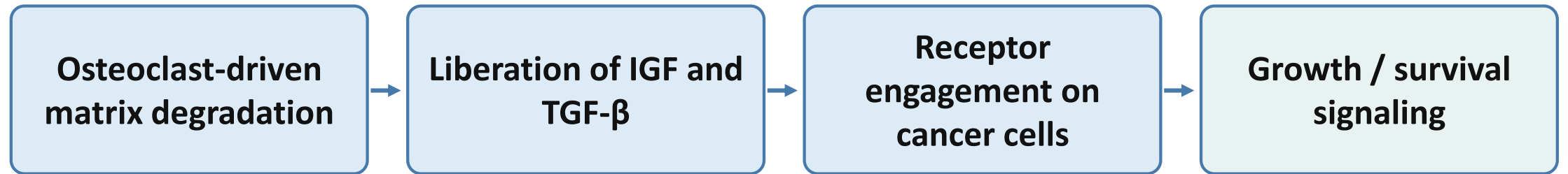
- Responds to tumor-secreted PTHRP.
- Increases RANKL expression.

### Osteoclast

- Activated by RANKL.
- Degrades bone matrix and frees embedded factors.

*Keep the direction of the signaling cascade explicit.*

## Bone matrix releases tumor-supporting factors



- These factors provide a route from host bone resorption back to cancer cells.

## The bone metastatic niche is a positive loop

- Tumor-secreted PTHRP activates an osteoblast–osteoclast circuit.
- Osteoclastic bone degradation releases matrix-bound growth factors.
- Growth-factor signals support cancer-cell survival and expansion.

*The loop illustrates reciprocal tumor–host conditioning, not a drug-treatment guideline.*

# Anatomic delivery and niche growth are separable

## Delivery to bone

- Cancer cells must circulate and reach the skeleton.
- Adhesion / extravasation are still required.

## Growth within bone

- Tumor and host bone cells exchange signals.
- Bone-resorption products support malignant growth.

*Reaching bone does not establish the PTHRP–RANKL loop by itself.*

## Application: A colon primary with liver deposits

**A patient with colon carcinoma develops metastatic deposits in the liver.**

1. What anatomical feature helps explain this distribution?

2. Why does first-pass delivery not prove colonization?

## Interpretation: Colon carcinoma and liver

- Portal venous drainage explains frequent initial delivery to the liver.
- Tumor cells must still survive, arrest, extravasate, and proliferate.
- The vascular pathway explains opportunity; Colonization requires tumor–organ compatibility.

*This pattern exemplifies, rather than exhausts, metastatic routing.*

## Application: Breast carcinoma with bone disease

**A patient with breast carcinoma develops an enlarging secondary lesion in bone.**

1. Which tumor-secreted factor can initiate the local feedback loop?

2. Which host cell releases matrix-embedded growth factors indirectly?

## Interpretation: The bone microenvironment

- Cancer-cell PTHRP stimulates osteoblast RANKL production.
- RANKL activates osteoclast-mediated matrix degradation.
- IGF and TGF- $\beta$  released from matrix stimulate cancer-cell signaling.

*This example shows reciprocal growth promotion in a permissive niche.*

## Application: Viable cells but no visible lesion

**Disseminated malignant cells are present, but no progressively enlarging distant deposit is evident.**

1. Which biological state may explain this observation?

2. What additional transition is needed for clinically apparent metastasis?

## Interpretation: Dormancy versus outgrowth

- Tumor dormancy allows survival in a distant tissue without productive growth.
- Escape from dormancy is required for expansion into an overt deposit.
- This distinction helps explain why dissemination and clinical metastasis diverge.

*The molecular trigger of dormancy escape is not established in the source.*

## Application: Metastasis despite atypical drainage

**A cancer disproportionately involves an organ not readily predicted by first-pass blood flow.**

1. What mechanisms beyond anatomy can explain the tropism?

2. Why might a richly perfused tissue remain metastasis-poor?

## Interpretation: Tropism and nonpermissive soil

- Endothelial adhesion ligands and tissue chemokines may guide tumor-cell homing.
- The local microenvironment may favor or resist subsequent growth.
- Skeletal muscle and spleen illustrate vascular abundance without high colonization.

*Tropism reflects both cell-intrinsic properties and host-organ biology.*

## Distinguish the principal stages at a glance

| Stage             | Core question               | Necessary biological task                  |
|-------------------|-----------------------------|--------------------------------------------|
| Circulation       | Can tumor cells survive?    | Resist shear, anoikis, host defenses       |
| Arrest and homing | Where do cells stop?        | Drainage plus specific tissue interactions |
| Extravasation     | Can cells enter the tissue? | Cross endothelium and basement membrane    |
| Colonization      | Can cells establish growth? | Adapt, shape niche, leave dormancy         |

*A tumor cell must successfully navigate several non-equivalent barriers.*

## Key mechanistic conclusions

- Clusters, platelet interactions, and possible fibrin deposition can aid circulation.
- Vascular anatomy, receptor–ligand tropism, and tissue “soil” determine destination.
- Extravasation is followed by an additional, often restrictive, growth challenge.
- Dormancy and tumor–stroma loops explain the gap between arrival and outgrowth.

*The metastatic cascade is a cooperative tumor–host process.*